While meeting with OHRP, it was suggested that the OIG talk with NIH to discuss the questions below. The OIG met with Dr. Kathy Hudson on July 19th to discuss these issues and she thought that it would be a good idea that they speak with you.

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- What was NIH's involvement in OHRP's review?
- Did NIH express any concerns about the informed consent document?
- From NIH's perspective, was the conduct of OHRP's review typical?

o Why or why not?

- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

Please let me know if your availability to meet with the OIG in a one-hour teleconference, which could potentially happen within the next week, or so.

Thanks in advance for your cooperation!

Tiffany Brown
NIH/OD/OMA
(301) 496-2464 - direct
(301) 402-0169 - fax

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Jarman, John (NIH/NICHD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)
Date: Monday, July 22, 2013 1:19:45 PM

Ok
Valerie Bonham from NIH OGC is available to speak with me today.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Jarman, John (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 1:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

I do not see any problems as long as you coordinate with OMA. thx

John S. Jarman
Associate Director for Administration/Executive Officer
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institutes of Health, DHHS
301-496-0648

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 9:04 AM
To: Jarman, John (NIH/NICHD) [E]
Subject: FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

John –
Is this ok?

thanks
Rose

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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 9:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Cc: Jarman, John (NIH/NICHD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Rose,
I see no problem with your meeting with the OIG, but you should check with John Jarman, just to clarify, before doing so.

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 8:55 AM
To: Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Subject: FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

FYI –

Is there someone that can let me know how these items are usually handled?

Thanks
Rose

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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 8:53 AM
To: Brown, Tiffany (NIH/OD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

HI
I am available:
July 23 – 9 am- 5 PM
July 24 – 9 am – noon
July 26 – 3-5 PM
July 29 – 10:30 am – 5 PM
July 30 – 10 am – 1 pm; 230 pm – 5 PM
Let me know if you need more options

Rose

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Brown, Tiffany (NIH/OD) [E]
Sent: Monday, July 22, 2013 8:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

DUE DATE: noon on July 23, 2013
ACTION: Please send your availability to meet with the OIG
CONTACT: Tiffany Brown, OMA, 301.496.2464

Good morning Dr. Higgins,

The OIG is currently conducting a study entitled, "*Office of Human Research Protections Oversight of the SUPPORT Clinical Trial*" (OEI-01-13-00420). This Congressionally requested study will examine the extent to which the Office for Human Research Protections (OHRP) followed procedures and exercised its discretion in its compliance evaluation of the SUPPORT clinical trial (start notice and study design attached).

While meeting with OHRP, it was suggested that the OIG talk with NIH to discuss the questions below. The OIG met with Dr. Kathy Hudson on July 19th to discuss these issues and she thought that it would be a good idea that they speak with you.

- When did NIH become aware of OHRP's review of the SUPPORT trial and UAB?
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    - Why or why not?
- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

Please let me know if your availability to meet with the OIG in a *one-hour teleconference*, which could potentially happen within the next week, or so.

Thanks in advance for your cooperation!

TIFFANY BROWN
NIH/OD/OMA
(301) 496-2464 - DIRECT
(301) 402-0169 - FAX

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)
Date: Monday, July 22, 2013 11:07:22 AM

Valerie Bonham and I contacted her this am – waiting to hear back

Rosemary D. Higgins, MD
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From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 11:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Honestly, this is a semi-legal proceeding. Tiffany works for OMA - -you should probably ask her who else will be in the meeting with you. Who were you working with in OGC, if anyone?

Lisa

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 8:55 AM
To: Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine

(NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]
Subject: FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

FYI –

Is there someone that can let me know how these items are usually handled?

Thanks

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 22, 2013 8:53 AM
To: Brown, Tiffany (NIH/OD) [E]
Subject: RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

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From: Brown, Tiffany (NIH/OD) [E]
Sent: Monday, July 22, 2013 8:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

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TIFFANY BROWN
NIH/OD/OMA
(301) 496-2464 - DIRECT
(301) 402-0169 - FAX

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bonham, Valerie (NIH/OD) [E]
Subject: Confidential:FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)
Date: Monday, July 22, 2013 9:28:50 AM
Attachments: 01-13-00420.Start notice.OHRP.SW.docx.pdf
SUPPORT Design Outline_6.4.docx
Information session 7.19.13 sign-in sheet.doc.pdf

Valerie

Would you have time for a brief call related to the attachments?

I am available today from 2-3 and 4-5 – let me know – I am teleworking from home.

Thanks

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Sent: Monday, July 22, 2013 8:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

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Thanks in advance for your cooperation!

TIFFANY BROWN
NIH/OD/OMA
(301) 496-2464 - DIRECT
(301) 402-0169 - FAX

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

OFFICE OF EVALUATION AND INSPECTIONS

MEMORANDUM

Date: May 23, 2013

To: Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
U.S. Department of Health and Human Services

From: David E. Tawes DET
Regional Inspector General
Office of Evaluation and Inspections
Office of Inspector General

Subject: Start Notice for Inspection: *Office of Human Research Protections Oversight of the SUPPORT Clinical Trial,* OEI 01-13-00420

Purpose of Inspection: This Congressionally requested study will determine the extent to which the Office for Human Research Protections (OHRP) followed procedures and exercised its discretion in its compliance evaluation of the SUPPORT clinical trial. We will determine what triggered OHRP to initiate its compliance evaluation of the SUPPORT clinical trial, as well as how it conducted its compliance evaluation. We will also determine the outcome of OHRP's compliance evaluation.

Background and General Description of Work: Section 289 of the Public Health Service Act authorizes OHRP to establish a compliance oversight process to review violations of human subjects protections in research conducted or supported by the Department of Health and Human Services. Pursuant to this authority, OHRP may receive complaints of such violations and can conduct for-cause compliance evaluations where it has jurisdiction. After receiving a complaint regarding the conduct of the SUPPORT clinical trial, a National Institutes of Health funded study on newborns, OHRP initiated a compliance evaluation in 2011 to review the conduct of the University of Alabama, Birmingham's (UAB) oversight of the Support clinical trial. It issued a determination letter against UAB in March of 2013. OEI will determine the extent to which OHRP followed its procedures in its compliance evaluation of the SUPPORT clinical trial.

Entrance Conference: An entrance conference will be scheduled as soon as possible. A draft inspection design will be provided with the entrance meeting notification.

OIG/OEI Headquarters Branch and Region: The Boston Regional office will conduct the inspection with the support of Headquarters' Evaluation Planning and Support Division. The team leader for this inspection is (b)(6) and the headquarters specialist is (b)(6) (b)(6) who may be reached at (b)(6)

cc: Kay Daly, Carla J. Lewis, and Maritza Hawrey, OAS; Pam Jones, GAO; Annette Johnson, ASPE; External Affairs; TSS; Region 1; (b)(6) Richard Stern; Marcia Sayer; Anne Gavin; Louise Schoggen; (b)(6); Vicki Robinson; ASFR; OHRP

Page 0013 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0014 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

OIG-NIH INFORMATOINAL MEETING: PARTICIPANT LIST

Office of Human Research Protections Oversight of the SUPPORT Clinical Trial

(OEI-01-13-00420)

July 19, 2013 (9:00AM – 10:00AM)

NAME	ORGANIZATION	EMAIL	PHONE#	INITIALS
Kathy Hudson	NIH/OD National Institutes of Health, Office of the Director Deputy Director for Science, Outreach, and Policy	fuchsb@mail.nih.gov	(301) 402-5225	KH
Meredith Stein	NIH/OD/OMA Office of Management Assessment Director, Division of Outside Review & Liaison and Division of Quality Management	steinme@mail.nih.gov	(301) 402-8482	*Via Phone*
Tiffany Brown	NIH/OD/OMA Management Analyst *Point of Contact for all NIH participants*	Brownty1@mail.nih.gov	(301) 496-2464	TB
Stephanie Devaney	NIH/OD Health Science Policy Analyst	devaneysa@mail.nih.gov	(301) 402-1994	SD
(b)(6)	OIG/OEI Office of Inspector General Office of Evaluations and Inspections Deputy Regional Director (Boston)	(b)(6)		
	OIG/OEI Assistant Inspector General for Evaluations			
	OIG/OEI Supervisory Program Analyst *Analyst-in-Charge*			
	GAO/OEI Program Analyst			

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nfiner@ucsd.edu"; "richard.ehrenkranz@yale.edu"; "Roger Faix (Roger.Faix@hsc.utah.edu)"; "Brad Yoder (Bradley.yoder@hsc.utah.edu)"; ""Duara, Shahnaz" (SDuara@med.miami.edu)"; "Frantz, Ivan"; "Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org)"; "Michael O"Shea (moshea@wakehealth.edu)"; "Phelps, Dale"
Cc: Archer, Stephanie (NIH/NICHD) [E]; " (mcunningham@rti.org)"; "Abhik Das (adas@rti.org)"
Subject: NRN SC meeting this week
Date: Monday, July 22, 2013 8:44:07 AM
Attachments: July_SC_Agenda_draft4.docx

TO SUPPORT INVESTIGATORS:

I have attached the NRN SC meeting agenda for later this week. We invite you to join two discussions:

1. Thursday July 25 at 10:30 am – Dr. Hudson
2. Friday July 26 at 2 pm – SUPPORT discussion
3. For those of you who knew Dr. Korones and want to stay on the call at 11 on Thursday, you are most welcome to attend.

Let me know if you have any questions. If you are having trouble calling in, please email Meg and I.

Dial:
Within the USA
(b)(6)

OR

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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NICHD Neonatal Research Network Steering Committee

RTI Offices, 6110 Executive Boulevard, Suite 902

Wednesday, July 24, 2013	
1:00 pm to 3:00 pm	Preemie Hypothermia Forms Training
3:00 pm to 5:00 pm	Coordinator's Meeting • Study updates • Regulatory binders • Consent burden • Coding CFM06 • INS-3 and study start-up • 21CRFpart11 Hospital EMR compliance • SAE clarifications (ongoing vs date resolved)

NICHD Neonatal Research Network Steering Committee

Neuroscience Center Building, 6001 Executive Boulevard Rockville, MD

Thursday, July 25, 2013	
8:30 am to 9:15 am	MILK Trial Subcommittee
9:15 am to 9:45 am	Hydrocortisone for BPD Subcommittee
9:45 am to 10:30 am	TOP Trial Subcommittee
10:30 am to 11:00 am	Kathy Hudson, PhD, Deputy Director for Science Outreach and Policy at NIH
11:00 am to 11:10 am	Remembrance of Dr. Shelley Korones – Dr. Tyson
11:10 am to 11:45 am	Optimizing Cooling Subcommittee
11:45 am to 12:30 pm	Preemie Hypothermia Protocol Training
12:30 pm	Lunch
1:00 pm to 1:45 pm	NEST Subcommittee
1:45pm to 2:30 pm	Cooling Neuro Certification Training (all certified examiners including GS should attend)
2:30 pm to 3:15 pm	Protocol: Low Dose Lipid – Dr. Calkins
3:15 pm to 4:00 pm	Concept: neonatal mortality-culture – Dr. Etchegaray
4:00 pm to 4:45 pm	Protocol: Incubator Weaning of Infants in the Moderate Preterm Registry (MPR): A Randomized Controlled Trial – Dr. Shankaran

NICHD Neonatal Research Network Steering Committee

Neuroscience Center Building, 6001 Executive Boulevard Rockville, MD

Friday, July 26, 2013		
8:15 am	Welcome and Introductions	Dr. Polin
8:20 am	NEST	Dr. Blakely
8:35 am	Coordinators Update	Cathy Grisby
8:45 am	Protocol Review	Dr. Poindexter
9:00 am	MILK	Dr. Colaizy
9:15 am	Optimizing Cooling and Secondaries	Dr. Shankaran, Van Meurs, Chalak
9:55 am	Publications	Dr. Sanchez
10:10 am	TOP	Dr. Bell
10:25 am	Moderate Preterm Registry	Dr. Walsh
10:40 am	Late Hypothermia	Dr. Laptook
10:55 am	ALPs Secondary	Dr. Laptook
11:15 am	Genomics	Dr. Cotten
11:30 am	GDB/EOS	Dr. Stoll
11:45 am	Hydrocortisone for BPD	Dr. Watterberg
12:00 pm	Term Hypotension	Dr. Fernandez
12:15 pm	Lunch	
1:00 pm	Preemie aEEG	Dr. Davis/Van Meurs
1:15 pm	Inositol	Dr. Phelps
1:30 pm	Concurrent Research Discussion	All
1:45 pm	SUPPORT School Age	Dr. Hintz
2:00 pm	SUPPORT	Drs. Carlo and Finer
2:30 pm	Follow-up	Dr. Higgins
2:45 pm	New Business and extra time	

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Cunningham, Meg"
Subject: RE: Updated NRN SC Agenda
Date: Monday, July 22, 2013 8:29:14 AM

I have invited Neil to Dr. Hudson's presentation and will invite the other SUPPORT investigators to that session, Shelley's remembrance and the SUPPRT discussion on Friday.

I will copy you

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Friday, July 19, 2013 5:55 PM
To: areynolds@upa.chob.edu; Avroy Fanaroff; Dan Elisbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; mgantz@rti.org; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; nambalavanan@peds.uab.edu; rohls@salud.unm.edu; Ronnie Guillet; Satyan Lakshminrusimha; Sood, Beena; soraya.abbasi@uphs.upenn.edu; Sudarshan Jadcherla; Jason.Etchegaray@uth.tmc.edu; KCalkins@mednet.ucla.edu; srhintz@stanford.edu; dale_phelps@urmc.rochester.edu; Marty Blakely; Roger.Faix@hsc.utah.edu; Finer, Neil; Erika Fernandez; barbara_stoll@oz.ped.emory.edu; alaptook@WIHRI.org; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; adas@rti.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; Aasma Chaudhary; ahensman@wihri.org; Ann_Scorsone@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; ciclark@med.unc.edu; Conra Lacy; mcunningham@rti.org; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; mcollins@peds.uab.edu; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; Teressa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin
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Subject: Updated NRN SC Agenda

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Hope you all have a great weekend!
Meg

Meg Cunningham, CCRP
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fax: 202-728-2095
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nfiner@ucsd.edu"
Subject: FW: Updated NRN SC Agenda
Date: Monday, July 22, 2013 8:27:21 AM
Attachments: July_SC_Agenda_draft4.docx

Neil

The SUPPORT discussion was added on Friday afternoon. Also, you may wish to join for Dr. Kathy Hudson's time slot on Thursday at 10:30 am – she is the first author (along with Drs. Guttmacher and Collins) of the NEJM piece that appeared in June 2013.

Regards

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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To: areynolds@upa.chob.edu; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; mgantz@rti.org; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; nambalavanan@peds.uab.edu; rohls@salud.unm.edu; Ronnie Guillet; Satyan Lakshminrusimha; Sood, Beena; soraya.abbasi@uphs.upenn.edu; Sudarshan Jadcherla; Jason.Etchegaray@uth.tmc.edu; KCalkins@mednet.ucla.edu; srhintz@stanford.edu; dale_phelps@urmc.rochester.edu; Marty Blakely; Roger.Faix@hsc.utah.edu; Finer, Neil; Erika Fernandez; barbara_stoll@oz.ped.emory.edu; alaptook@WIHRI.org; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; adas@rti.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.; Aasma Chaudhary; ahensman@wihri.org; Ann_Scorsone@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; awilliams@upa.chob.edu; Bethany Ball; cathy.grisby@uc.edu; Cheri Gauldin; clclark@med.unc.edu; Conra Lacy; mcunningham@rti.org; Dara Cucinotta; Dee Maffett; Diana Vasil; Donia Campbell; Estelle Fischer; Faithe Hamer; Gabrio, Jenna; gennie_bose@med.unc.edu; Georgia.E.McDavid@uth.tmc.edu; Hale, Ellen; Holly Wadkins; Huitema, Carolyn Petrie; Janice Bernhart; janice_wereszczak@med.unc.edu; Joanne R Finkle; Johnson, Karen; Julianne Hunn; Julie Gutentag; Kimberley.fisher@duke.edu; ldw@iu.edu; Lewis-Evans, Amanda; Lizette.Torres@UTSouthwestern.edu; mcollins@peds.uab.edu; msacilowski@upa.chob.edu; nancy newman; Newman, Jamie; Patty Luzader; Peter Beshay; rbara@med.wayne.edu; RGeller@mednet.ucla.edu; Rosemary Jensen; Shirley Cosby; Stephanie Guilford; Teressa Chanlaw; tiwussow@salud.unm.edu; Toni Mancini; Zaterka-Baxter, Kristin
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Meg

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Phelps, Dale"
Subject: FW: Updated NRN SC Agenda
Date: Monday, July 22, 2013 8:25:31 AM
Attachments: July_SC_Agenda_draft4.docx

Dale

Here is the agenda for this week's SC meeting – please note, INS and concurrent research are together on Friday. If you have any trouble connecting to the call in line, please email Meg and I.

Thanks

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Meg

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fax: 202-728-2095
www.rti.org

From: Roger Faix
To: Laptook, Abbot; Cunningham, Meg; Hensman, Angelita
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Preemie Hypo MOP - 1 last issue
Date: Friday, July 19, 2013 1:53:52 PM

Many thanks to everyone for all of your continuing contributions. I was in (b)(6) (b)(6) this past week with no/minimal e-mail availability and opened this string of e-mails only today. I agree with all of everyone's input.

Roger

PS: Rose, what are the times and dates of the presentations re: the study at the steering committee? Also, is there a number for calling in? I would like to be available/join discussion as needed, if I am not already obligated here.

From: Laptook, Abbot [ALaptook@Wihri.org]
Sent: Monday, July 15, 2013 7:49 PM
To: Cunningham, Meg; Roger Faix; Hensman, Angelita
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Preemie Hypo MOP - 1 last issue

I will mention the issue of participation in follow-up as a potential benefit when this is presented at the SC; we discussed this on the LH call and felt we should leave it in the consent as written. Tx, AL

From: Cunningham, Meg [mcunningham@rti.org]
Sent: Monday, July 15, 2013 8:42 AM
To: Roger.Faix@hsc.utah.edu; Laptook, Abbot; Hensman, Angelita
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Preemie Hypo MOP - 1 last issue

Hi All,

I have all the materials ready to post. However, in the manual for the following SAE's, nobody has provided any text. If someone can send this to me in the next few hours, I can add this and get all posted before I leave at 1:00 pm ET for a trip.

6. NEC
7. Perforations, ulcerations or bleeding from the esophageal probe
8. Hyperglycemia
9. Hypoglycemia
10. PPHN Developed after randomization

Also, in the consent in the manual, I removed this sentence. Participating in the follow-up part of this study may benefit your child with the early detection and referral for treatment of any developing problems.

Thanks,
Meg

Meg Cunningham, CCRP
RTI International

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From: D'Angio, Carl
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Guillet, Ronnie
Subject: FW: ASBH
Date: Friday, July 19, 2013 12:38:26 PM
Attachments: wilfond shepardOHRP2013.2.doc

Rose,

Thanks for your time on the telephone today.

Attached please find the request I received to be the presenter who meets the objective of "Understand[ing] the objectives of the SUPPORT study and the study design."

As we discussed, I would not use any data or information that were not in the public domain and not express any opinions on behalf of myself, my University or the NRN regarding the ethics of the study or OHRP's determination. I would confine myself to laying out the scientific background. I would, of course, disclose my relationship to the NRN and to the trial.

If you feel this needs NRN Steering Committee discussion, please feel free to bring it to the Steering Committee. I'd welcome any input.

As we also discussed, I have been asked to represent the University of Rochester at the HHS Public Meeting on August 28. At present, our spoken comments are likely to be confined to technical issues regarding cluster randomized comparative effectiveness trials.

Thanks again for your help.

Carl

Carl T. D'Angio, MD
Professor of Pediatrics and Medical Humanities & Bioethics
Director, Neonatal Clinical Research
Director, Ethics Key Function, URMC CTSI
Division of Neonatology, Golisano Children's Hospital
University of Rochester Medical Center
601 Elmwood Avenue, Box 651
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Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Wilfond, Benjamin [mailto:benjamin.wilfond@seattlechildrens.org]
Sent: Tuesday, July 16, 2013 8:17 PM
To: D'Angio, Carl
Subject: ASBH

Carl
Are you going to ASBH?
I got approval to organize a presentation on the support study, and I initially contacted Sad Sayeed, but he was not going but was willing to come for this talk but suggested that we look elsewhere?
Would you be interested in joining this panel? Your role would be to present the "facts" of the study and would involve creating and reviewing your slides with Nancy an me before hand.
I was going to contact Alan Fleischman but I get the impression that you have a emerging interest in this, so wanted to support that interest

Benjamin Wilfond MD
Director | Treuman Katz Center for Pediatric Bioethics
Seattle Children's Research Institute
Professor | Department of Pediatrics
University of Washington School of Medicine

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WWW seattlechildrens.org/bioethics

"OHRP and SUPPORT--Different Views"

The SUPPORT study, which compared different target oxygen saturations levels in premature infants, was controversial because of a lack of consensus about key issues related to risk, parental permission, and the role of oversight. Much of the controversy centers on how federal regulations for the protection of human subjects should be applied to research randomizing participants to two or more interventions considered to be within the standard of care in the non-research context. Differing views on how to understand and communicate the risks and potential benefits of research enrollment in such studies resulted in two groups of bioethicists expressing opposing views about the determination by the Office for Human Research Protections that researchers in the SUPPORT study failed to disclose reasonably foreseeable risks in the parental permission process. This session will explore these issues and provide the audience with an opportunity to collectively explore these differing views. The first speaker will provide background information about the study and the next two speakers will explain why they see this case differently. The second half of the session will be a facilitated discussion by the moderator.

Objective(s):
1. Understand the objectives of the SUPPORT study and the study design.
2. Explore why some bioethicists believe that the approach to parental permission fell below the regulatory threshold and that the OHRP's determination was justified.
3. Explore why some believe that the approach to parental permission did not fall below the regulatory threshold and that the OHRP's determination was not justified.

Nancy M.P. King JD, Wake Forest School of Medicine and Wake Forest University
Sadeth Sayeed MD JD, Harvard University and Boston Children's Hospital
Benjamin S. Wilfond MD, University of Washington and Seattle Children's Hospital
Lois Shepherd JD, University of Virginia School of Medicine and School of Law

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Cunningham, Meg"
Subject: RE: clintrials number
Date: Friday, July 19, 2013 10:59:19 AM
Attachments: Re ct.gov.msg

Dr. Hirschfeld is working on the results reporting

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Friday, July 19, 2013 10:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: clintrials number

FYI – I can't submit this until we work out the issues of results reporting!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 19, 2013 8:35 AM
To: Cunningham, Meg; kwatterberg@salud.unm.edu
Cc: Newman, Jamie
Subject: RE: clintrials number

Looks fine to me

Thasnk
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Friday, July 19, 2013 8:32 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; kwatterberg@salud.unm.edu
Cc: Newman, Jamie
Subject: FW: clintrials number

Please see the short description I plan to add below, highlighted in yellow. Please let me know if you have any changes.

Extended follow-up: Subjects enrolled in the Neuroimaging/MRI secondary study will also be seen for a follow-up visit at 6-7 years to look at later school-age development. Secondary studies in this cohort will evaluate the incidences of overweight and obesity by a body mass index (BMI), determine rates of hypertension, and evaluate the relationship of adrenal function to cardiovascular risk factors.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 18, 2013 12:05 PM
To: 'Kristi Watterberg'
Cc: Cunningham, Meg
Subject: RE: clintrials number

Yes a short description can be added as was done for FU and extended FU:

Follow-up: Subjects will be seen for a follow-up visit at 18-22 months corrected age to look at neurodevelopment.

Extended follow-up: Subjects enrolled in the Neuroimaging/MRI secondary study will also be seen for a follow-up visit at 6-7 years to look at later school-age development.

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higginsr@mail.nih.gov

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Thursday, July 18, 2013 11:57 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: clintrials number

Will the information be updated to include the adrenal secondary?

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 7/17/2013 3:33 PM >>>
Same number

Sent from my iPhone

On Jul 17, 2013, at 5:09 PM, "Kristi Watterberg" <KWatterberg@salud.unm.edu> wrote:

> Hi, Rose - will the adrenal study get its own clinical trials number, or be added to the existing NEURO study?
>
> thanks, Kristi

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"; Hirschfeld, Steven (NIH/NICHD) [E]
Cc: "Cunningham, Meg"; "Gantz, Marie"; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: ct.gov
Date: Friday, July 19, 2013 10:00:30 AM

Steven –
Can you help RTI with entering results from the SUPPORT Trial – see below
Thanks
Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, July 19, 2013 9:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Cunningham, Meg; Gantz, Marie
Subject: ct.gov

Rose:

We continue to have problems trying to enter the SUPPORT trial results into clinicaltrials.gov. As you know, while SUPPORT had a 2X2 factorial design, we were not powered to look at interaction between the 2 factors (in other words, within-table analysis comparing the 4 groups – low sat/CPAP, high sat/CPAP, low sat/surf, high sat/surf). Rather, we were only powered to look at the marginal comparisons (CPAP vs surf and low vs high sat), and all our publications have done just that, consistent with the trial protocol. However, clinicaltrials.gov does not seem to be set up to accept the results of such factorial design trials (most of which are not powered to look at interactions, just like SUPPORT). It either asks for results across the 4 groups (which we don't want to do because that is not how the trial was powered or reported in the literature) or, when we try to enter the marginal results, it assumes that we have twice the sample size than we actually had. So, we are sort of at a loss on how to proceed and would like your advice.

Thanks a lot

Abhik

Abhik Das, Ph.D.
Senior Research Statistician
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e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Kennedy, Kathleen A
To: Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: ROP Secondary Paper Submission
Date: Thursday, July 18, 2013 1:59:18 PM
Attachments: ROP Natural History Study Manuscript (final revision with longer abstract for J Perinatol, no figures, with comments).doc
Figure 2.pdf
Figure 1.pdf
Figure 4.pdf
Figure 3.pdf

It took me a little while to jump through all the hoops for the electronic submission but I finally got it submitted. I was able to make the abstract a little longer (the allowance was more words than I thought) so I added back some of the text from previous versions. Here's what was submitted.

Thanks for all your help with this.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
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6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy, MD MPH[1]; Lisa A. Wrage, MPH[2]; Rosemary D. Higgins, MD[3] Neil N. Finer, MD[4]; Waldemar A. Carlo, MD[5]; Michele C. Walsh, MD MS[6]; Abbot R. Laptook, MD[7]; Roger G. Faix, MD[8]; Bradley A. Yoder, MD[8]; Kurt Schibler, MD[9]; Marie G. Gantz, PhD[2]; Abhik Das, PhD[10]; Nancy S. Newman, RN[6]; Wade Rich, RRT[4]; Dale L. Phelps, MD[11]; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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Running title: Retinopathy of Prematurity Screening Criteria

Funding source: The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT trial.

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Abstract

Objective: To determine if current retinopathy of prematurity screening guidelines adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

Study Design: Data from the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used. Inborn infants 24 $^{0}/_{7}$ to 27 $^{6}/_{7}$ weeks gestational age with consent prior to delivery were enrolled in 2005-2009. Severe retinopathy of prematurity (Type 1 retinopathy of prematurity or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the randomized trial. Examinations followed then current American Academy of Pediatrics screening recommendations.

Results: 1316 infants were enrolled in the trial. 997 of the 1121 who survived to first eye exam had final retinopathy of prematurity outcome determined. 137 met criteria for severe retinopathy of prematurity and 128 (93%) of those had sufficient data (without missing or delayed exams) to determine age of onset of severe retinopathy of prematurity. Postmenstrual age at onset was 32.1 to 53.1 wks. In this referral center cohort, 1.4% developed severe retinopathy of prematurity after discharge.

Conclusion: Our contemporary data support the 2013 screening guidelines. Some infants do not meet treatment criteria until after discharge home.

Keywords (not in title): extremely premature infant

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines[1],[2] are based on natural history data from the CRYO-ROP[3] and LIGHT-ROP[4] studies. The CRYO-ROP study[5] remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.[6] Over the past two decades, survival of lower birth weight infants in the US and other developed countries has increased.[7,8] For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.[7] The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age.[3] It rarely occurs before 30 weeks postmenstrual age (PMA, sum of GA at birth and chronological age) or before 4 weeks chronological age. Current American Academy of Pediatrics (AAP) recommendations are for screening to begin by 31 weeks PMA for infants born at 22-27 weeks.[1] The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.[4] Based on the results of the ET-ROP trial, treatment is now recommended for Type 1 ROP, defined as stage 3 in zone I or plus disease with any ROP in zone I, or stage 2 or 3 with plus disease in zone II. Since Type 1 ROP occurs earlier in the course than CRYO-ROP threshold ROP, it is important to determine if screening criteria developed for CRYO-ROP threshold ROP are still appropriate for reliable timely

identification of Type 1 ROP.[9] There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial[10] and a population-based cohort study of infants born 2004-2007 in Sweden[11] reported the age of onset of stages 1, 2, and 3 ROP; however, the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from Canada reported the age of onset of Type 1 ROP in a cohort of 214 infants $\leq$ 27 weeks gestation;[12] this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort[13] reported that "No preterm infants required treatment before the 33rd postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for severe ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 $^{6}/_{7}$ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)[14] to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O_2 saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants.[14] Inborn infants $24\ ^{0}/_{7}$ – $27\ ^{6}/_{7}$ weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 31-33 weeks postmenstrual age, as recommended in the AAP guidelines in place when the study began.[15,16] Subsequent inpatient and outpatient exams were conducted according to the ophthalmologists' established screening procedures at each center. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Study eye exam data were recorded for each exam until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up (including exams after hospital discharge) was curtailed at 55 wks PMA.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the postmenstrual or chronological age at which ROP or ROP of a given severity was detected, with the recognition that onset was some

time prior to detection. Infants with Type 1 ROP whose first exam with Type 1 ROP was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. No infants had Type 1 ROP on the initial exam. Infants who did not complete exams according to the study schedule (adjudicated ROP outcomes) were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for continuous data grouped into quantiles.[17] Cumulative incidence curves for age of onset of severe ROP and age of maturity were compared by gestational age subgroups (26-27 weeks vs 24-25 weeks) using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-four percent (643/997) of these infants developed ROP and 14% (137/997) developed severe ROP. Among infants with severe ROP, 93% (128/137) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-

Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for ROP are shown in Table 2.[18;19,20] Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p<0.05$ for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3. For the 9 infants with severe ROP and uncertain age of onset, the age of identification ranged from 33.7-40.0 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (lower oxygen saturation and higher oxygen saturation target ranges) and the distributions were similar so only the combined data are shown. The distributions for age of onset of severe ROP for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to prior studies,[3] our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. PMA of onset of severe ROP is significantly later for GA groups 26-27 weeks vs. 24-25 weeks ($p<0.01$). There is no significant difference in the distribution of chronologic age of onset between these two GA groups.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had

mild or moderate ROP (ROP that did not meet criteria for severe ROP). The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but we did not identify any no risk factors in our data that clearly identify infants at risk to develop severe ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,[9] so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies[3] in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,[3] lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation by the AAP that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,[1] albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.[21] Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age[22] and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to

chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,[11] which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al[12] included 23-27 week infants; infants ≤25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (24-25 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest ages of onset of Type 1 ROP are more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,[12] the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al[13] that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged

or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study has several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.[23] The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Current AAP screening guidelines, published in 2013,[1] recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines. In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.[23]

Acknowledgments

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Deanne E. Wilson-Costello, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kimberly Yolton, PhD; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; Anna M. Dusick, MD FAAP; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; Susan R. Hintz, MD MS Epi; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; Elisabeth C. McGowan, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Myriam Peralta-Carcelen, MD MPH; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Yvonne E. Vaucher, MD MPH; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Cheryl Runyan; James Wilkes; Paul Zlotnik.

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University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Janell Fuller, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Gary David Markowitz, MD; Gary J. Myers, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Roy J. Heyne, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Jon E. Tyson, MD MPH; Patricia W. Evans, MD; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita

Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Anna Bodnar, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

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Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

Conflict of Interest: The authors declare that they have no financial interests related to the work described in this manuscript.

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Figure Legends:

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all SUPPORT trial infants with known outcome (997 survivors + 223 infants who died)

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP[1] Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/ Moderate ROP	Severe (Type 1 or Treated) ROP
n	1316	997	354	506	137
Gestational age, wks [mean (SD[2])]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.4 (0.9)
Birth weight, g [mean (SD)]	830 (193)	849 (190)	943 (173)	823 (180)	704 (142)
Small for gestational age[3] [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	154 (44)	179 (35)	41 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (45)
Hispanic	259 (20)	190 (19)	69 (19)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (57)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	341 (96)	480 (95)	134 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

[1] Retinopathy of prematurity
[2] Standard deviation
[3] Based on Olsen[24] growth curves

Table 2. Risk factors for ROP[1]

Risk Factor	No ROP[2]	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	354	506	137
Days on supplemental oxygen[3] [median (IQR[4])]	33 (10, 60)	59 (31, 94)	95 (68, 119)
Late-onset sepsis (+ culture) [(n (%)]	75 (21)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	15[5] (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	69[5] (14)	29 (21)
Proven necrotizing enterocolitis[6] [n (%)]	20 (6)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	123 (35)	271 (54)	94 (69)

[1] Retinopathy of prematurity
[2] $p<0.05$ for all comparisons of No ROP vs Any ROP (mild, moderate, or severe)
[3] Tabulated until 120 days or discharge if discharged sooner, among infants who survived to discharge, transfer or 120 days
[4] Interquartile range
[5] Missing data for 1 infant
[6] Modified Bell's stage II or III[25]

Table 3. Postmenstrual and chronological age of onset[1] [with 95% confidence intervals (CI[2])] of any stage ROP[3] (among infants with ROP age of onset determined)

		Postmenstrual Age (weeks)								
ROP type	n	Min[4]	1%	5%	25%	50%	75%	95%	99%	Max[4]
Any ROP (95%CI)	634	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP[5] (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

		Chronological Age (weeks)								
ROP type	n	Min	1%	5%	25%	50%	75%	95%	99%	Max
Any ROP (95%CI)	634	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP[3] (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

(95% CI)										

[1] Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.
[2] Confidence interval
[3] Retinopathy of prematurity
[4] Min = minimum age at which designated severity of ROP was identified; max = maximum age.
[5] Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP[1] criteria in relation to discharge and transfer

Infants with Severe ROP N=137	First exam with severe ROP occurred before discharge to home n=123	First exam with severe ROP criteria occurred after discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks [median, range]	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks [median, range]	42.5 (37.7-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital [n]	1	4

[1] Retinopathy of prematurity

Table 5. ROP[1] exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

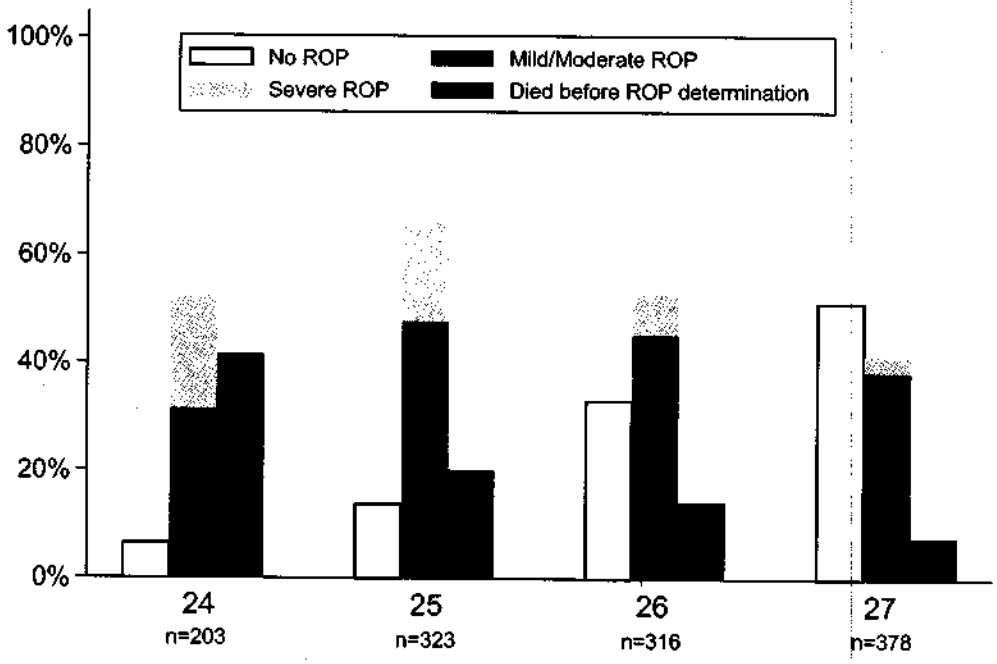
Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I [n (%)]	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone [n (%)]	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP [n (%)]	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone [n (%)]	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP [n (%)]	0	121 (23%)
Plus disease [n (%)]	0	0
No exam prior to discharge [n (%)]	0	3
Unknown (missing or incomplete information on exam prior to discharge) [n (%)]	0	5

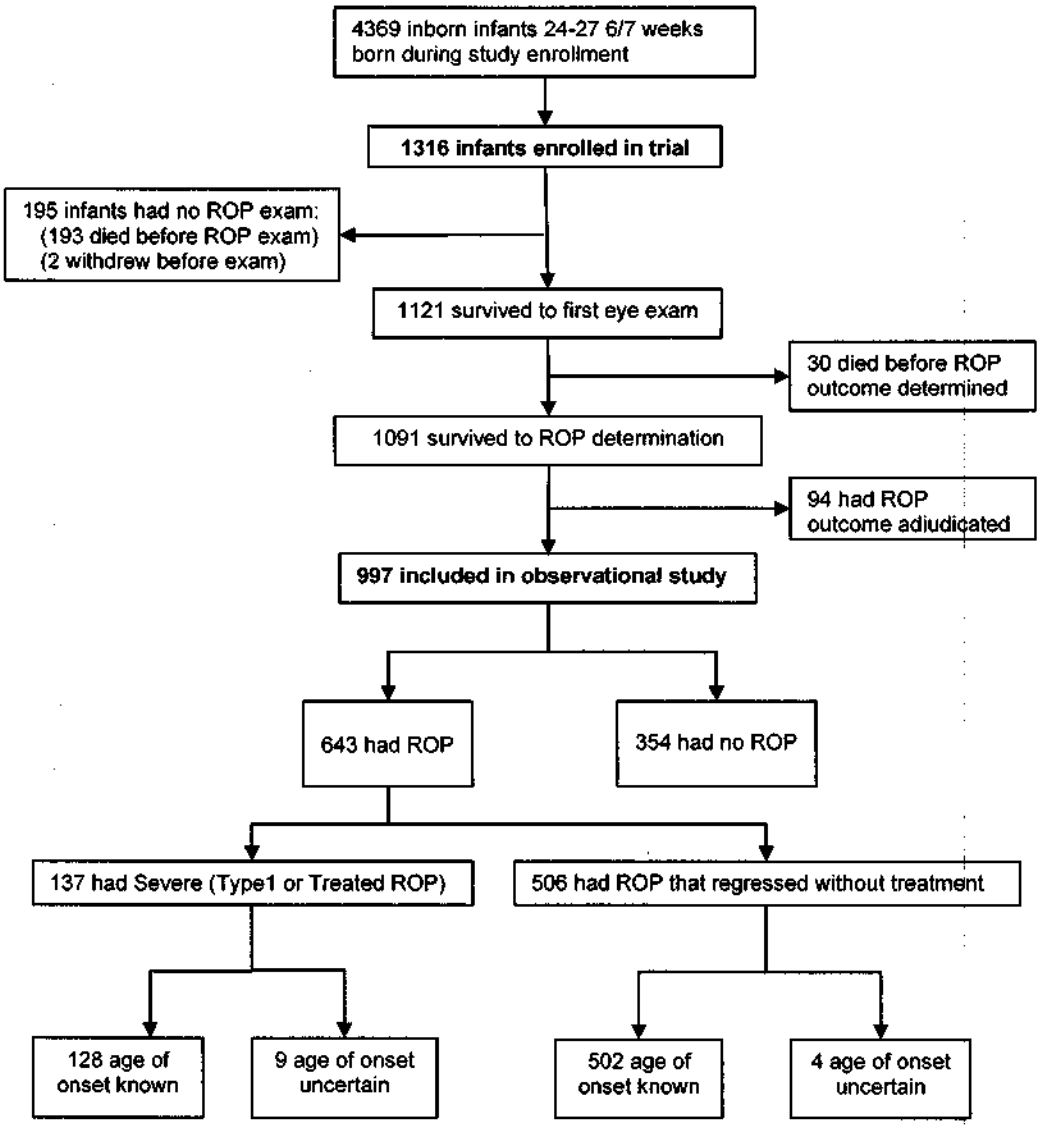
[1] Retinopathy of prematurity

Table 6. Risk factors for ROP[1] for infants with final ROP status determined after discharge home

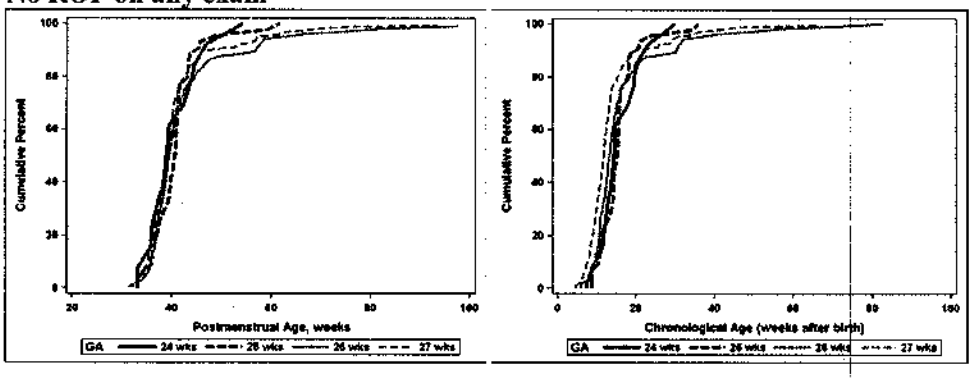
Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, g [mean (SD)]	701 (103)	872 (185)
GA[2] at birth, wks [mean (SD)]	25.7 (0.9)	26.4 (1.0)
Days on oxygen [mean (SD)]	59 (27)	47 (33)
Early onset sepsis [n (%)]	0	10 (2)
Late onset sepsis [n (%)]	7 (50)	148 (28)
Fungal sepsis [n (%)]	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	0	59 (11.1)
Proven necrotizing enterocolitis [n (%)]	1 (7)	36 (7)
Patent ductus arteriosus [n (%)]	11 (79)	258 (48)
Discharge on oxygen [n (%)]	2 (14)	88 (16)

[1] Retinopathy of prematurity
[2] Gestational age

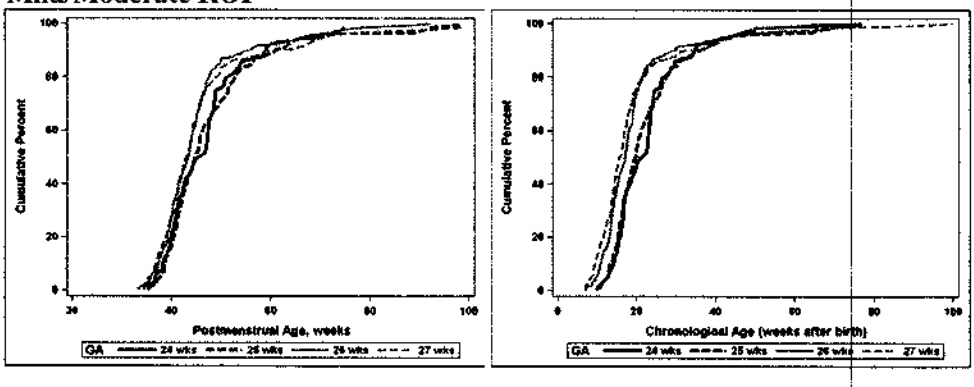


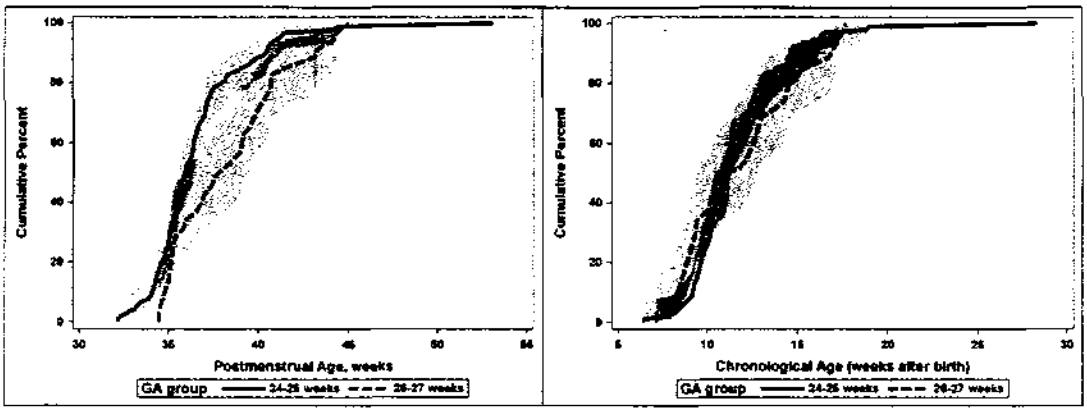


No ROP on any exam



Mild/Moderate ROP





From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bonham, Valerie (NIH/OD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Date: Thursday, July 18, 2013 10:23:06 AM
Attachments: 01-13-00420.Start notice.OHRP.SW.docx.pdf
ATT00001.htm
SUPPORT Study crucial studies...fragile subjects001.pdf
ATT00002.htm

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From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, July 10, 2013 1:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Jarman, John (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

FYI...nothing needs doing at this point, but wanted you to know.

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, July 10, 2013 12:24 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Fwd: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

From: "Barros, Colleen (NIH/OD) [E]" <BarrosC@od.nih.gov>
Date: July 9, 2013, 1:01:01 PM EDT
To: "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>, "Tabak, Lawrence (NIH/OD) [E]" <Lawrence.Tabak@nih.gov>
Cc: "Servis, Suzanne (NIH/OD) [E]" <ServisS@OD.NIH.GOV>, "Barros, Colleen (NIH/OD) [E]" <BarrosC@od.nih.gov>
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Kathy-----perhaps this one got by you. Can you let us know? The IG contacted us again about a contact point as they want to start. Larry thought it should be you but please let us know if you think it should be someone else. Thanks.

From: Barros, Colleen (NIH/OD) [E]
Sent: Friday, June 28, 2013 1:16 PM
To: Tabak, Lawrence (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Barros, Colleen (NIH/OD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Importance: High

Kathy-----I spoke to Larry re this. He thought it might be you as contact point. Agree? Short fuse.

From: Servis, Suzanne (NIH/OD) [E]
Sent: Thursday, June 27, 2013 4:29 PM
To: Barros, Colleen (NIH/OD) [E]
Cc: Stein, Meredith (NIH/OD) [E]; Allen, Gail (NIH/OD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Importance: High

ISSUE: Who at NIH should talk to the OIG about the SUPPORT Study?

Colleen, attached and included below is info about a new review by the OIG Office of Evaluations and Inspections related to the SUPPORT Study (see attached NYT article to refresh your memory). The OIG inspectors are asking to talk to the following NIH officials the week of July 7 (!):

- Francis S. Collins, M.D., Ph.D.,
- Alan E. Guttmacher, M.D.,
- Kathy L. Hudson, Ph.D., and
- Rosemary Higgins, M.D.

They will ask them the following questions:

- When did NIH become aware of OHRP's review of the SUPPORT trial

and UAB?

- What was NIH's involvement in OHRP's review?
- Did NIH express any concerns about the informed consent document?
- From NIH's perspective, was the conduct of OHRP's review typical?
    - Why or why not?
- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

I am asking your advice about who at NIH should talk to the OIG Inspectors. We can discuss at your convenience, although it sounds like the OIG would like to move quickly. Thank you, Suzanne

Suzanne J. Servis
Director, Office of Management Assessment
Office of the Director
National Institutes of Health
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Phone: 301-496-1873
Fax: 301-480-1204

From: Brown, Tiffany (NIH/OD) [E]
Sent: Thursday, June 27, 2013 4:14 PM
To: Servis, Suzanne (NIH/OD) [E]
Cc: Monickam, Sarah (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]
Subject: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Hi Suzanne,

Per our discussion, I am attaching the information on the OIG's upcoming review entitled, "*Office of Human Research Protections Oversight of the SUPPORT Clinical Trial*" (OEI-01-13-00420). Please let Meredith and myself know the outcome of your discussion with Colleen.

I know that you said that you didn't really need the memo, but I included the link, for your convenience:
http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf.

This is the request from the OIG (start notice is attached):

OIG is currently conducting a study, *Office for Human Research Protections Oversight of*

the SUPPORT Clinical Trial, (OEI-01-13-00420). This Congressionally requested study will examine the extent to which the Office for Human Research Protections (OHRP) followed procedures and exercised its discretion in its compliance evaluation of the SUPPORT clinical trial (start notice attached). As a part of this review, we would like to meet with NIH to discuss its role in OHRP's oversight of the SUPPORT trial and the University of Alabama Birmingham (UAB). We are available to meet the week of July 7th (except, Tuesday, July 9th).

We would like to meet with the following NIH officials:

- Francis S. Collins, M.D., Ph.D.,
- Alan E. Guttmacher, M.D.,
- Kathy L. Hudson, Ph.D., and
- Rosemary Higgins, M.D.

Our general questions include the following:

- When did NIH become aware of OHRP's review of the SUPPORT trial and UAB?
- What was NIH's involvement in OHRP's review?
- Did NIH express any concerns about the informed consent document?
- From NIH's perspective, was the conduct of OHRP's review typical?
    - Why or why not?
- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

Thanks!

TIFFANY BROWN
NIH/OD/OMA
(301) 496-2464 - DIRECT
(301) 402-0169 - FAX

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

OFFICE OF EVALUATION AND INSPECTIONS

MEMORANDUM

Date: May 23, 2013

To: Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
U.S. Department of Health and Human Services

From: David E. Tawes DET
Regional Inspector General
Office of Evaluation and Inspections
Office of Inspector General

Subject: Start Notice for Inspection: *Office of Human Research Protections Oversight of the SUPPORT Clinical Trial,* OEI 01-13-00420

Purpose of Inspection: This Congressionally requested study will determine the extent to which the Office for Human Research Protections (OHRP) followed procedures and exercised its discretion in its compliance evaluation of the SUPPORT clinical trial. We will determine what triggered OHRP to initiate its compliance evaluation of the SUPPORT clinical trial, as well as how it conducted its compliance evaluation. We will also determine the outcome of OHRP's compliance evaluation.

Background and General Description of Work: Section 289 of the Public Health Service Act authorizes OHRP to establish a compliance oversight process to review violations of human subjects protections in research conducted or supported by the Department of Health and Human Services. Pursuant to this authority, OHRP may receive complaints of such violations and can conduct for-cause compliance evaluations where it has jurisdiction. After receiving a complaint regarding the conduct of the SUPPORT clinical trial, a National Institutes of Health funded study on newborns, OHRP initiated a compliance evaluation in 2011 to review the conduct of the University of Alabama, Birmingham's (UAB) oversight of the Support clinical trial. It issued a determination letter against UAB in March of 2013. OEI will determine the extent to which OHRP followed its procedures in its compliance evaluation of the SUPPORT clinical trial.

Entrance Conference: An entrance conference will be scheduled as soon as possible. A draft inspection design will be provided with the entrance meeting notification.

OIG/OEI Headquarters Branch and Region: The Boston Regional office will conduct the inspection with the support of Headquarters' Evaluation Planning and Support Division. The team leader for this inspection is (b)(6) and the headquarters specialist is (b)(6) (b)(6) who may be reached at (b)(6)

cc: Kay Daly, Carla J. Lewis, and Maritza Hawrey, OAS; Pam Jones, GAO; Annette Johnson, ASPE; External Affairs; TSS; Region 1; (b)(6) Richard Stern; Marcia Sayer; Anne Gavin; Louise Schoggen; (b)(6) Vicki Robinson; ASFR; OHRP

The New York Times

April 15, 2013

Crucial Studies, Fragile Subjects

By SABRINA TAVERNISE

WASHINGTON — How much oxygen should a premature baby be given in the first days and weeks of life? Neonatologists have been trying to answer that question since the 1940s, sometimes with disastrous results.

Premature infants need oxygen because their lungs are not fully formed, but early attempts to save lives by turning up oxygen inadvertently caused blindness in many babies.

"They did a lot of damage before they realized what was going on," said Arthur L. Caplan, head of the division of medical ethics at NYU Langone Medical Center.

That experience has cast a long shadow over subsequent efforts to pioneer medical interventions for newborns. And the issue arose again last week when it came to light that a federal watchdog agency, the Office for Human Research Protections, had formally notified a network of 23 major research institutions that they had failed to warn parents about the risks of their infants' participation in a large oxygen study.

The underlying ethical question remains: How do researchers balance protecting these most vulnerable patients from the risks of medical studies with the potential benefits of such research for all premature babies?

The purpose of the study, known as Support, was to find the sweet spot for oxygen concentration in an infant. The American Academy of Pediatrics had set the standard treatment at a band between 85 and 95 percent, and researchers were trying to determine what part of that was optimal.

The goal was laudable, the federal watchdog said, but the method was not. Researchers randomly assigned infants to two groups, with half the children to get an oxygen concentration on the low end, 85 percent to 89 percent, and the other half to get 91 percent to 95 percent, on the high end. But the researchers did not explain to parents in consent forms that the risk of an eye disease, retinopathy of prematurity, was greater in the higher oxygen group. Based on past studies, there was reason to expect that infants in the upper band would be at higher risk. Indeed, the results found that infants in the upper band

developed eye disease at more than twice the rate of those in the lower band — 18 percent compared with 9 percent.

"Based on their very hypothesis, they were thinking that there might well be a difference," said Dr. Jerry A. Menikoff, the director of the Office for Human Research Protections. "Being in the higher end should have put you at greater risk of developing eye disease."

The study's designers agreed that the risk of blindness should have been more clearly explained, but said that the infants were within the standard band of care, and therefore facing the same steep odds as any premature infant not in the study.

Dr. Menikoff disagreed.

"To be told that this was all standard care — it wasn't," he said. "It was taking a child and flipping a coin and giving them 50 percent chance of being at the higher end and 50 percent chance of being at the lower end. They were changing what happened to all of the children."

Some experts contend that there is a lot of guesswork in oxygen care because there still is no established evidence for a particular level of concentration and that the risks were effectively the same for infants in the study as those outside it.

"A really honest clinician just flips a coin in his head," said David C. Magnus, a professor of pediatrics and the director of the Stanford Center for Biomedical Ethics. "Physicians could have their own views, but there was no evidence supporting any given spot on the band."

In the late 1990s, neonatologists began calling for systematic studies to establish that evidence. Dr. Ola Didrik Saugstad, a professor of pediatrics at the University of Oslo, who is an expert in neonatology and oxygen, said there had been about 12 studies since. Among them were three large clinical trials involving thousands of babies, including the Support study.

The Support study's results, published in 2010, surprised researchers. Infants in the lower oxygen band had a higher mortality rate — 20 percent — than those in the higher one — 16 percent. The finding has had a profound effect on medical practice.

"We changed our practices immediately, almost overnight," said Dr. Saugstad, who did not participate in the study. "We increased saturation targets again."

The letter from the watchdog agency said that brain injury and death were clear risks for the low-oxygen group, and that in addition to the risk of blindness, parents should have been notified of those too.

But Dr. Neil Finer, the study's principal investigator, who is a professor emeritus at the University of California, San Diego, said there had been nothing to suggest that the lower end of the standard band would cause higher mortality, and therefore it was impossible to warn parents.

"When we designed that study, there was no information from anywhere to suggest that you'd have increased mortality if you stayed within the range," he said.

Still, the risk of blindness was not unknown, and Dr. Menikoff called it "deeply troubling" that 23 institutions did not catch the failure to warn parents about it. In terms of punishment — which can range from institutions offering corrective action to their being forbidden to use government grants for research with human subjects — he said "everything is on the table."

Dr. Menikoff added: "My goal is to make sure the parents are appropriately protected. It's not too much to expect."

But Dr. Magnus argued that the move by the agency would have a chilling effect. Such clinical trials are so difficult to get off the ground and can add such valuable scientific knowledge that raising what he argues are unnecessary alarms will hold back innovation.

"Making research that's not risky sound risky means we'll be doing medicine based on hunches, who the doctor trained with, and which drug company gives away the best gifts," Dr. Magnus said. "I'm very worried about what this will mean for research that tries to answer the question: Of the things we are now doing, which one is best?"

Dr. Saugstad, the Norwegian expert, said that the warning about the consent forms was concerning, and that scientists and neonatologists would be discussing it at a meeting in Washington this month.

"I was really surprised when I read about it," he said. "I thought that everything had been done in a very careful way. And apparently it had not. We really have to think once again about how to do this in a proper way."

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bonham, Valerie (NIH/OD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Thursday, July 18, 2013 10:11:18 AM
Attachments: 130607_Letter to SUPPORT Study Investigators Requesting Study Data_FINAL_Signed.doc
Carome response v1.docx
Importance: High

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, July 15, 2013 1:33 PM
To: barbara_stoll@oz.ped.emory.edu; alaptook@WIHRI.org; Anne Marie Reynolds; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; adas@rti.org; mgantz@rti.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; Satyan Lakshminrusimha; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.
Cc: Finer, Neil; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; Ivan.Frantz@childrens.harvard.edu; SDuara@med.miami.edu; moshea@wfubmc.edu
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Importance: High

Hello All:

At its previous monthly call, the steering committee wanted us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have written the attached draft response that has been vetted by the legal folks at RTI. Neil, Wally and Rose have also looked at this text. Please take a look and let me know your feedback by July 22. We can then finalize and send the response.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu

Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

June 7, 2013

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
3040 East Cornwallis Road
Post Office Box 12194
Research Triangle Park, NC 27709-2194

Waldemar A. Carlo, M.D.
Director, Division of Neonatology
University of Alabama at Birmingham
Women & Infants Center
1700 6th Avenue
South Birmingham, AL 35233

Neil N. Finer, M.D.
Chief, Division of Neonatology
Department of Pediatrics
School of Medicine
University of California, San Diego
3020 Children's Way, MC 5109
San Diego, CA 92123-5109

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Drs. Das, Carlo, and Finer:

In accordance with the National Institutes of Health's (NIH's) long-standing data sharing policy,[1] which requires data sharing for all NIH-funded grants, Public Citizen's Health Research Group respectfully requests a digital copy of all individual subject-level data — without subject identifiers — obtained for the SUPPORT study that was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The data being requested includes the data on actual oxygen saturation levels that were achieved for each subject over the course of their involvement in the study. We are seeking all data for (a) the 1,316 subjects enrolled and randomly assigned to one of the four experimental groups in the SUPPORT study; and (b) those subjects who were eligible to be, but were not, enrolled in the SUPPORT study, and for whom

[1] National Institutes of Health. NIH Data Sharing Policy and Implementation Guidance. March 5, 2003. http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. Accessed June 6, 2013.

data was collected and published regarding demographics, baseline clinical characteristics, and clinical outcomes.[2]

We also respectfully request that you provide with the data (a) an explanation of the format used for storing the data; (b) a description of how the data was coded; and (c) the case report forms for each subject.

Thank you for your prompt attention to this request. Please notify us immediately if you have any questions about the data we are seeking or anticipate problems fulfilling our request.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Senior Advisor and Founder
Public Citizen's Health Research Group

cc: Dr. Allan Guttmacher, Director, National Institute of Child Health and Human Development

[2] Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics.* March 2012;129(3):480-484.

July 8, 2013

Michael A. Carome, M.D.
Director, Public Citizen's Health Research Group
Washington, DC.

Dear Sir:

In reference to your letter dated June 7, 2013, and on behalf of the NICHD Neonatal Research Network (NRN) Steering Committee, we are currently unable to entertain your request for access to data collected for the NRN Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). The principal reasons behind this decision are as follows:

1. As mentioned in the clinicaltrials.gov citation for this trial, extended follow-up at school age for a cohort of children enrolled in SUPPORT is still ongoing. Thus, in accordance with the NIH guidance referenced in your letter, we have no plans to share the data from this study before the follow up portion of the study is complete and the final results have been published in a peer reviewed journal.
2. The following policies enshrined in the Network's Policies and Procedures charter guide the NRN in responding to requests from external scientific investigators:
   "From time-to-time, the NRN receives requests from non-Network researchers for protocol documents (protocol, manual, and forms) and study data for pre-specified purposes. All requests should be sent to the NICHD Program Scientist for consideration. Generally, data are not released until two years following publication of a primary study.
   Depending on the nature of the request, it may go to the Data Access Subcommittee or directly to the Steering Committee. The Steering Committee votes to approve release of the requested information. The external requestor is asked to acknowledge the use of the NICHD Neonatal Research Network materials in all relevant applications, presentations, and publications."
   Typically, the Steering Committee requires a scientific protocol with stated hypotheses, specific aims, background and significance and a reasonably detailed study design and analysis plan, as well as a budget to entertain such external requests.
3. As per the data sharing plan proposed by the NRN Data Coordinating Center (DCC) and approved by NIH, if external data sharing is approved by the NRN Steering Committee and NICHD, the DCC will create de-identified limited-access data sets for this purpose. Although the data sets will be stripped of identifiers and otherwise modified to prevent easy identification of patients in the study, the narrow focus of the population to be analyzed and the possible rarity of some outcome measures and risk factors might make it possible for an identification to be made. Therefore, in order to protect the confidentiality and privacy of the subjects, external investigators granted access to these data must adhere to strict requirements defined by the NRN Steering Committee that are incorporated into a standard Data Distribution Agreement to which all external investigators seeking the data must agree to abide and adhere to. The Data

Distribution Agreement may be subject to review by the legal departments and IRBs of the DCC and the NRN clinical centers, and must be approved by the Steering Committee. Finally, in accordance with NICHD policies, outside researchers will be required to submit an approval from their IRB.

In summary, in accordance with NIH approved policies, we will not be presently releasing the requested data from the SUPPORT trial. Once the extended follow up for the SUPPORT trial concludes and its primary results are published, the NRN will be happy to entertain scientifically rigorous protocols that seek access to the trial data to conduct secondary analyses that may contribute to the science of neonatology. Such requests will need to follow established data sharing policies adopted by the NRN and NIH and adhere to required human subjects protections, as referred to earlier in this letter.

Please let us know if there are any questions.

Sincerely

Abhik Das

Waldemar Carlo

Neil Finer

for the NICHD Neonatal Research Network Steering Committee

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bonham, Valerie (NIH/OD) [E]
Subject: RE: (b)(5)
(b)(5)
Date: Thursday, July 18, 2013 9:56:37 AM

I have a meeting at 11 am (open until then but would be tight for you to get over here). I also have a meeting until 4 PM.

I am available tomorrow until 2 pm and could come over to you in the am - let me know what works the best.

Regards
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Bonham, Valerie (NIH/OD) [E]
Sent: Thursday, July 18, 2013 9:52 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: (b)(5)
(b)(5)

Rose -- It might be better to meet face to face. How hard would that be for you this morning? I could come to Exec Blvd.

Valerie Bonham, J.D.
301-451-8351 (direct)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, July 17, 2013 2:21 PM
To: Bonham, Valerie (NIH/OD) [E]
Subject: RE: (b)(5)
(b)(5)

Today 4-5 pm
Tomorrow before 11 am or 4-5 pm

Thanks for getting back to me

Regards
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Bonham, Valerie (NIH/OD) [E]
Sent: Wednesday, July 17, 2013 12:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: (b)(5)
(b)(5)

Hi Rosemary,

I was out of the country and am just back. Do you have some to talk this afternoon or tomorrow?

Val

Valerie Bonham, J.D.
301-451-8351 (direct)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, July 12, 2013 10:05 AM
To: Bonham, Valerie (NIH/OD) [E]
Subject: FW: (b)(5)
(b)(5)

Valerie -
Not sure if you had a chance to look into this question, but I would like to get an opinion from you.
Thanks for your help
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, June 27, 2013 10:40 AM

To: Bonham, Valerie (NIH/OD) [E]
Subject: RE: (b)(5)
(b)(5)

I have a quick question (b)(5) - Our steering committee controls data and requests (by vote). However, we have 4 sites that are no longer in the network that generated data for the SUPPORT trial and 4 new sites (now steering committee members) who did not contribute any data. The network is reconfigured every 5 years based on grant applications to the RFA. (b)(5)
(b)(5)

Some of the new sites feel they (b)(5)
(b)(5)

Thanks for your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Bonham, Valerie (NIH/OD) [E]
Sent: Thursday, June 13, 2013 10:04 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: (b)(5)
(b)(5)

Perfect. Thanks.

Valerie Bonham, J.D.
301-451-8351 (direct)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, June 13, 2013 9:55 AM
To: Bonham, Valerie (NIH/OD) [E]
Subject: Re: (b)(5)
(b)(5)

How about 2 pm?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Bonham, Valerie (NIH/OD) [E]
Sent: Thursday, June 13, 2013 09:45 AM
To: Higgins, Rosemary (NIH/NICHD) [E]

Subject: RE: (b)(5)
(b)(5)

Yes, afternoon?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, June 13, 2013 9:41 AM
To: Bonham, Valerie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Subject: Re: (b)(5)
(b)(5)

Not today - are you available tomorrow?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Bonham, Valerie (NIH/OD) [E]
Sent: Thursday, June 13, 2013 08:50 AM
To: McGarey, Barbara (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: (b)(5)
(b)(5)

Hi Dr. Higgins,

Please forgive my delay in connecting. Do you have time to talk today?

Val

From: McGarey, Barbara (NIH/OD) [E]
Sent: Wednesday, June 12, 2013 11:37 AM
To: Bonham, Valerie (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: (b)(5)
(b)(5)

Hi Val, Dr. Higgins is requesting (b)(5) that I think you are best positioned to answer going forward. I'll drop by and brief you on it. Julie is aware you'll be handling so just coordinate as needed if any (b)(5)

Thanks,

Barb

Barbara M. McGarey, J.D.
Deputy Associate General Counsel for Public Health, NIH Office of the General Counsel, PHD, NIH Branch
31 Center Drive, Rm 2B-50
Bethesda, MD 20892-2111
(301) 496-6043 (phone)
(301) 402-1034 (fax)
mcgareyb@od.nih.gov<mailto:mcgareyb@od.nih.gov>

From: Higgins, Rosemary (NIH/NICHD) [E]

Sent: Tuesday, June 11, 2013 5:13 PM
To: McGarey, Barbara (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: FW: (b)(5)
(b)(5)

Here is the data access guidelines and the section of the grant from the RTI DCC application. Let me know what you think.
Thanks for your help.
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:03 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: (b)(5)
(b)(5)

Hi
(b)(5)

(b)(5)

Let me know if there are questions.
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Guttmacher, Alan (NIH/NICHD) [E]

Sent: Monday, June 10, 2013 7:41 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: (b)(5)

(b)(5)

More on the most recent info request, which did not come to us, of course (we were only cc:ed), but only to the investigators and RTI…

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, June 09, 2013 10:16 PM
To: Muroff, Julie (NIH/OD) [E]
Cc: McGarey, Barbara (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]
Subject: Re: (b)(5)

(b)(5)

Thank you so much Julie. It is ironic that the (b)(5)

(b)(5) I guess that is why our jobs are quietly entertaining.

I am sharing via cc your opinion with pat white and Alan Guttmacher. (For reasons I do not understand my iPhone thinks Alan should be with caps but not pat.).

Alan - we look forward to response from nichd. pat, we look forward to an explanation of why your name is not capitalized.

Warmly,
Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov<mailto:kathy.hudson@nih.gov>

On Jun 9, 2013, at 7:51 PM, "Muroff, Julie (NIH/OD) [E]" <muroffj@od.nih.gov<mailto:muroffj@od.nih.gov>> wrote:

(b)(5)

(b)(5) We would be happy to elaborate by phone or meeting.

Julie A. Muroff, J.D., LL.M.
Senior Attorney
HHS Office of the General Counsel, PHD, NIH Branch

31 Center Drive, Bldg. 31, Rm.2B-47
Bethesda, MD 20892
301-451-4910 (direct)
301-402-1034 (Fax)
Julie_Muroff@nih.gov<mailto:Julie_Muroff@nih.gov>

From: McGarey, Barbara (NIH/OD) [E]
Sent: Friday, June 07, 2013 10:47 PM
To: Rockey, Sally (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: Re: (b)(5)
(b)(5)

From: Rockey, Sally (NIH/OD) [E]
Sent: Friday, June 07, 2013 09:58 PM
To: Hudson, Kathy (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

(b)(5)

Sally J. Rockey, Ph.D.
NIH Deputy Director for Extramural Research OD/NIH/DHHS One Center Drive Building 1, Room 144 Bethesda, MD 20892
301-496-1096 (BLDG. 1)
301-435-2698 (ROCK I)
301-402-3469 Fax
rockeysa@od.nih.gov<mailto:rockeysa@od.nih.gov>

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, June 07, 2013 9:29 PM
To: Rockey, Sally (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing I am thinking
(b)(5)
(b)(5) Do you agree?

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, June 07, 2013 5:19 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

FYI…

Alan

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: adas@rti.org<mailto:adas@rti.org>; wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>; nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org<mailto:mcarome@citizen.org>
web: www.citizen.org<http://www.citizen.org/>

From: McGowan, Elisabeth C
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Wednesday, July 17, 2013 2:40:44 PM

Thank you Abhik. I think the letter is appropriate, well stated and very strong.

Liz

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, July 16, 2013 9:52 AM
To: McGowan, Elisabeth C
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dr. McGowan:

Sorry to have missed you in the initial email. Please let me know if you have any comments.

Thanks

Abhik

From: Das, Abhik
Sent: Monday, July 15, 2013 1:33 PM
To: '[SCRN] Stoll, Barbara (barbara_stoll@oz.ped.emory.edu)'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Anne Marie Reynolds'; 'Barbara Schmidt'; 'Bell, Edward'; 'Bill Truog'; 'Brenda Poindexter (bpoindex@iu.edu)'; 'Carl D'Angio'; 'Das, Abhik (adas@rti.org)'; 'Gantz, Marie (mgantz@rti.org)'; 'goldb008@mc.duke.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'Leif Nelin'; 'mcw3@cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'RAP32@columbia.edu'; 'Satyan Lakshminrusimha'; 'sshankar@med.wayne.edu'; 'Uday Devaskar'; 'vanmeurs@leland.stanford.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'
Cc: Finer, Neil; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Ivan Frantz (Ivan.Frantz@childrens.harvard.edu) (Ivan.Frantz@childrens.harvard.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Importance: High

Hello All:

At its previous monthly call, the steering committee wanted us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have written the attached draft response that has been vetted by the legal folks at RTI. Neil, Wally and Rose have also looked at this text. Please take a look and let me know your feedback by July 22. We can then finalize and send the response.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, July 17, 2013 8:51 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Mona requested these article links – Dr. Wolfe states:

Given that there were almost identical studies, coordinated with the SUPPORT group, in the UK, Australia, New Zealand, Canada, and other countries that have similar, if not identical regulation of human research, it is surprising that, to our knowledge, government authorities in those countries have not investigated the adequacy of those consent forms.

Full text is at:
http://www.bmj.com/content/347/bmj.f4198?view=long&pmid=23838555

Two current responses at:
http://www.bmj.com/content/347/bmj.f4198?tab=responses

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 12:36 PM
To: Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

I love it!

Alan

From: Bock, Robert (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 12:36 PM

To: Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

"Joy vey"

when something awesome and fantastic happens. opposite of oy vey.
"i just made a 100% on my history test, yo!"
-"joy vey, man!"

http://www.urbandictionary.com/define.php?term=joy%20vey

I wasn't happy with the Trayvon Martin verdict, and I'm certainly not happy with the sequester, but, Geez, isn't this a great country? The way our culture borrows from other cultures to come up with something new and cool never ceases to amaze me.

And, I'm also happy that Sid Wolfe didn't mention support on Diane Rehm.

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:44 AM
To: Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

That would, indeed, be the opposite of "oy vey" (aren't we multicultural)

Alan

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:43 AM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Re: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Wahooo

Catherine Y Spong MD
Associate Director for Extramural Research
Director, Division of Extramural Research
NICHD, NIH
6100 Executive Blvd Rm 4A05A Bethesda MD 20892
Spongc@mail.nih.gov
Phone 301 435 6894

On Jul 16, 2013, at 11:42 AM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

> Its over and we are clear
>
> *Mona*
>
> Mona Jaffe Rowe, M.C.P.
> Associate Director for Science Policy,
> Analysis and Communication
> *Eunice Kennedy Shriver* National Institute of

Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:38 AM
To: Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Oy vey...

Alan

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:36 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Wolfe is stepped down as director of Health Research at Public Citizen and Carome took his place- this is a recent event. He specifically recruited Carome. Wolfe will continue to work on drug approvals and adverse reaction issues.

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:23 AM
To: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Thanks for the updates!

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
31 Center Drive
Building 31, Room 2A03

Bethesda, MD 20892-2425

Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:21 AM
To: Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

So far nothing has been said about SUPPORT——just wanted you all to know since we were going this live now – wrote to Calvin and suggested that he check in with Kathy H too – hoping this is all moot anyway

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
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National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 11:12 AM
To: Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Thanks – agree with concern of getting in an on-air exchange; depending how it goes maybe we can work to get air time on Diane Rehm to explain the other side?

From: Rowe, Mona (NIH/NICHD) [E]

Sent: Tuesday, July 16, 2013 11:10 AM
To: Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: FW: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

FYI—Cathy and Alan – You can see that Calvin wrote and was concerned that the they may bring up the SUPPORT trial- -and wanted Rose to be on hand—rose is in a meeting that she cannot leave—Marian is listening and if we need to ask Rose a question or have her listen we take her out of the meeting for a few meetings.

I spoke to Calvin and said however – that my gut is that we would not necessarily want to respond on the line and get into some exchange on the air with Sidney. And I asked if we could even do respond instantaneously on the line without clearance?

I am also going to write to Calvin and have him speak to Kathy. Meanwhile at a minimum – we are listening

Mona

Mona Jaffe Rowe, M.C.P.
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National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Jackson, Calvin (NIH/OD) [E]
Sent: Tuesday, July 16, 2013 10:33 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Thanks Mona,

I don't think (b)(5) ..

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, July 16, 2013 10:32 AM
To: Jackson, Calvin (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

HI Calvin –just getting out of meeting – let me see about contacting Rose

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Jackson, Calvin (NIH/OD) [E]
Sent: Tuesday, July 16, 2013 9:38 AM
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: Dr. Sidney Wolfe on The Diane Rehm Show today at 11AM

Hi Mona and Bob,

Dr. Sidney Wolfe will be today's guest on The Diane Rehm Show at 11:00 a.m. Dr. Collins thinks that Dr. Wolfe may (b)(5) (although the description of the program below indicates that he'll be discussing the drug approval process, drug safety and his 40-year career as a consumer health advocate.

Consumers may soon have more safety information about generic drugs, and they may also have the ability to sue manufacturers if they experience an adverse reaction. Dr Sid Wolfe says these changes are long overdue. As founder and senior adviser of the nonprofit advocacy organization Public Citizen, these are among hundreds of changes he's pushed for over the last four decades. His best-selling book, "Worst Pills, Best Pills," first published in 1988, details critical safety information on common prescription drugs. Dr. Sid Wolfe talks about the drug approval process, drug safety and his 40-year career as a consumer health advocate.

I will record the show and provide a digital copy to all who want it. Dr. Collins also wanted to know if Rosemary Higgins would be available to listen in and perhaps even call in if the lines are opened to callers. Again, Dr. Wolfe may not (b)(5) but we want to be prepared (just in case). You can listen to The Diane Rehm Show at: http://thedianerehmshow.org/. Thanks,

Calvin

Calvin Jackson
Deputy Associate Director for Communications and Public Liaison
National Institutes of Health
Building 1, Rm. 350
Bethesda, MD 20892
phone: 301-594-8750
(NIH cell): 301-905-2664
email: cj8e@nih.gov

From: Wally Carlo, M.D.
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; kurt.schibler@cchmc.org; Abbot Laptook; mcw3@cwru.edu; Yvonne Vaucher; Myriam Peralta, M.D.; Roger.Faix@hsc.utah.edu; Bradley.yoder@hsc.utah.edu; Gantz, Marie; Wallace, Dennis; nxs5@case.edu; Wade RIch
Cc: Archer, Stephanie (NIH/NICHD) [E]; SDuara@med.miami.edu; CNavarrete@med.miami.edu; Wrage, Lisa Ann
Subject: RE: Publications | Navarrete
Date: Tuesday, July 16, 2013 7:43:17 PM
Attachments: Manuscript Growth Outcomes SUPPORT 7 2013 ADwc.docx

I have added my comments to those of Abhik.

Great progress but I think we need to add more on the growth velocities particularly in relation to the distribution of the caloric intake.

Wally
-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, July 16, 2013 3:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; nfiner@ucsd.edu; kurt.schibler@cchmc.org; Abbot Laptook; mcw3@cwru.edu; Yvonne Vaucher; Myriam Peralta, M.D.; Roger.Faix@hsc.utah.edu; Bradley.yoder@hsc.utah.edu; Gantz, Marie; Wallace, Dennis; nxs5@case.edu; Wade RIch
Cc: Archer, Stephanie (NIH/NICHD) [E]; SDuara@med.miami.edu; CNavarrete@med.miami.edu; Wrage, Lisa Ann
Subject: RE: Publications | Navarrete

Here are my comments.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 12, 2013 12:40 PM
To: Wally Carlo, M.D.; nfiner@ucsd.edu; Kurt Schibler [kurt.schibler@cchmc.org]; Abbot Laptook; Michele Walsh (mcw3@cwru.edu); Yvonne Vaucher; mperalta@peds.uab.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Gantz, Marie; Das, Abhik; Wallace, Dennis; nxs5@case.edu; Wade RIch
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Duara, Shahnaz' (SDuara@med.miami.edu); Cristina Navarrete (CNavarrete@med.miami.edu)
Subject: FW: Publications | Navarrete

Hi
Here is the SUPPORT Growth secondary paper. Please send your comments to Shahnaz and Tina (Copied on the cc line) by July 26.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]
Sent: Friday, July 12, 2013 12:17 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: 'Shahnaz Duara (sduara@miami.edu)'; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Publications | Navarrete

Hello Stephanie!
Here's the copy of the long overdue manuscript for review of the subcommittee.
I apologise for the delay.
Cristina

>

Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

Cristina T Navarrete[1], Lisa A Wrage[2], Shahnaz Duara[1], on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network. University of Miami, Miami, FL[1]; Research Triangle Institute International, RTP, NC[2]; NICHD, Rockville, MD

Abstract:

BACKGROUND: Post-natal growth restriction is a common ~~major~~ morbidity in preterm infants. ~~O~~Perturbations in oxygenation may influence somatic growth, and recent observational study reported less growth failure with lower oxygen saturation (SpO2) targets but conflicting effects have been reported; ~~a recent observational study showed that infants exposed to higher oxygen saturation (SpO2) targets experience poorer growth (Tin, Arch Child Dis FN 2001). The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) showed that the lower target range of SpO2 from birth, as compared to the higher range, resulted in less retinopathy of prematurity in survivors but an increase in mortality (Carlo, NEJM 2010). However, it is not known what the impact of~~whether ~~assignment to these different saturation targets immediately after birth would have any impact on postnatal growth~~.

OBJECTIVE: To test the hypotheses that infants maintained in the lower SpO2 target range while on supplemental oxygen from birth will have less~~better~~ growth failure (<10th percentile) at 36 weeks post-menstrual age (PMA) and at 18-22 months corrected age (CA) ~~(fewer babies <10th percentile% for weight),~~ and better growth trajectories from birth to 18-22 months CA.

METHODS: A sub-group of 810 preterm infants from the SUPPORT trial, randomized at birth to lower (85-89%, n=402, GA 26.~~2~~ ± 1.~~1~~wks, BW 83~~98.6~~ ± 186 gm) ~~and~~ or higher (91-95%, n=408, GA 26.~~2~~ ± 1.~~1~~wks, BW 84~~039.6~~ ± 191gm) SpO2 target ranges were studied. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28; 32 and 36

Comment [WC1]: Too long (336 words) so I cut it to get under 250.

Comment [WC2]: But the Askie RCT designed to test growth effects showed no effect.

Formatted: Superscript

weeks PMA, and at 18-22 months corrected age. Growth velocities were estimated ~~for each randomization group~~ using the exponential method~~,~~ and analyzed using linear mixed models. Poor growth outcome, defined as weight < 10th percentile~~%ile~~ at 36 weeks PMA and 18-22 months CA, was ~~analyzed~~ compared across the two treatment groups using robust Poisson regression.

RESULTS: Growth outcomes including growth at 36 weeks PMA and 18-22 months CA, as well as growth velocity ~~was~~ were not different between the lower and higher SpO2 target groups. ~~In this large subgroup, mortality was not different between groups at 36 weeks PMA and, both, growth at 36 wks PMA and at 18-22 month were not different between the two groups.~~

CONCLUSION: Differential~~Early~~ oxygen saturation targeting in the standard of care range did not impact growth velocity or growth failure in preterm infants, ~~receiving supplemental oxygen in accordance to~~ with ~~the requirements of the SUPPORT trial~~.

Comment [AD3]: I strongly feel that we should not get into the mortality issue here because (a) it was not a stated outcome for this study, and (b) we don't want to contradict our own findings from the main trial.

Introduction:

The improved survival of extremely low gestational age infants highlights ~~a new problem,~~ the significant incidence of growth restriction seen around the age of term equivalence[1] that persists until later in childhood[2]. The incidence of postnatal growth restriction (weight less than the tenth percentile for postmenstrual age at the time of hospital discharge) has been described to range anywhere from 79% [1] to 99% [3], when using fetal-infant growth curves. ~~The consequence of~~ pPoor postnatal growth is associated ~~includes~~with poorer neuro-developmental outcome[2, 4] as well as an increased risk in adulthood for metabolic syndrome and type 2 diabetes if there is subsequent catch-up growth[5].

Comment [WC4]: This implies a causal relationship but that has not been proven.

The recent emphasis on the provision of early and adequate nutritional support recognizes the associa~~connec~~tion between nutrition and growth[6-8]. However, when Embleton *et al* followed infants prospectively, they were able to attribute only 45% of variance in weight gain to energy intake deficits[9], suggesting that postnatal growth is influenced by factors beyond caloric intake. Tissue oxygenation has often been postulated to be amongst these factors[10-15]. Animal studies investigating this possibility have shown species-specific outcomes, with rat pups raised in hypoxic conditions after birth showing a reduced body mass, while hamster pups raised in the same condition have growth unaffected [10]. In humans, the relationship between oxygenation and postnatal growth is not well~~still not fully~~ understood. Infants with established bronchopulmonary dysplasia (BPD) have slower growth velocities when weaned off supplemental oxygen at discharge [11, 12]; whereas those discharged on home oxygen have either

better growth [13,14] or no difference in growth[15]. For preterm infants without BPD, assignment to different saturation targets starting several weeks after birth did not impact later growth[16,17]. On retrospective observation of neonatal units with differing oxygen saturation targeting policies, infants in the neonatal intensive care unit (NICU) with lower saturation targets incidentally had better in-hospital growth[18], suggesting that higher oxygen saturation may play in role in creating postnatal growth restriction. The design of the NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial (SUPPORT) offered a novel~~n~~ opportunity to investigate this possibility in a randomized and controlled fashion from the time of birth~~h, which is something that has never been done before~~[19,20]. We hypothesized that infants enrolled in SUPPORT assigned to the lower saturation target group would have better growth velocity and less growth failure in hospital and at 18-22 months corrected age.

Methods:

Sample: Our sample is composed of a subgroup of infants enrolled in SUPPORT, a ~~prospective~~ 2 x 2 factorial, randomized trial. The oxygen saturation targeting arm of SUPPORT was designed to determine whether exposure to a lower saturation target soon after birth, within the accepted normal range at the time, was associated with a lower incidence of severe retinopathy of prematurity ~~and~~/or death before discharge from the hospital. Between February 2005 and February 2009, women delivering between 24 weeks 0 days and 27 weeks 6 days of gestation were asked to enroll in the study at participating centers. Infants were randomized to either lower (85-89%) or higher (91-95%) saturation target arms within the accepted oxygen saturation range the first two hours after birth. Electronically altered pulse oximeters (Massimo™)~~,~~ for masking~~,~~ were used for both groups until 36 weeks postmenstrual age (PMA)

Comment [AD5]: Should we mention that this was not an intentional subgroup, but just a product of the timing of approval for this secondary study?

Comment [WC6]: I would mention the CPAP intervention before this sentence.

or until the infant was breathing ambient air and off positive pressure support for more than 72 hours.

This study protocol was approved by the institutional review board of all the 15 participating centers, and written informed consent was obtained from each infant's parent/guardian before any measurements were taken for analysis. In addition to the patient descriptors collected in the main trial[19], select anthropometric measurements and nutrition snapshots were collected by research nurses at each institution. Measurements were obtained at birth, weekly for the first 4 weeks, ~~and again~~ at 32 and 36 weeks PMA, and at 18-22 month follow-up, I, ~~if~~ the infant was deemed stable; weight was obtained using the bedside scale, length was measured using the Preemie Length Board™ and head circumference was measured using a tape measure. Each measurement was obtained twice and then averaged. Detailed 24-hour nutritional data were collected weekly for the first 4 weeks and then at 32 and 36 weeks PMA by chart review ~~at time of discharge~~. Type and volume of intravenous solutions, including composition of parenteral nutrition, and type and volume of enteral feedings, including modular additives, were recorded. Composition of milk formula and breast milk (mother's own or donor) was based on the assumed average composition of breast milk and the manufacturer's product information for the various milk formulas. Research nurses used standardized study forms while collecting information and all data were subsequently transmitted to the central NRN data-coordinating center at RTI International.

The primary outcome measures were the combined outcome of growth failure, defined as weight less than 10th percentile, or death, at 36 weeks PMA and at 18-22 month follow-up, and in-hospital growth velocities. The reference growth standards used were the gender-specific

Comment [AD7]: Did we just look at in-hospital velocities and not up to 18-22 months? This seems to be contradicted in the next sentence.

intrauterine growth curves of Olsen[21] for in-hospital growth and the WHO Growth Curves[22] for 18-22 month growth.

Statistical Analysis: Clinical characteristics and outcomes for infants in the higher and lower oxygen saturation target groups were compared using linear mixed models for continuous variables and robust Poisson regression for binary outcomes, adjusting for multiple birth clustering and ~~SUPPORT~~ trial stratification variables (gestational age group and center). An unadjusted Wilcoxon rank sum test was used for skewed continuous variables. In-hospital growth velocity was calculated using the exponential method[23]. Post-hoc analysis of actual median saturations while on supplemental oxygen allowed the study population as a whole to be divided into quartiles and assessed for mortality and growth. Severity of illness (defined as FiO2 > 0.4 and mechanical ventilation for more than 8 hours in the first 15 days) according to quartile of actual median saturation was analyzed by Chi-square tests. Primary outcomes were analyzed by quartile using robust Poisson regression with results expressed as adjusted relative risks and 95% confidence intervals. All analyses were performed using SAS version 9.3 at RTI International.

Comment [AD8]: Need to define what these are.

Results:

A total of 1,316 infants were enrolled in SUPPORT (FIGURE 1); of these, 810 infants were consented ~~enrolled in~~ for the Growth Secondary Study. Of the enrolled infants, 681 infants survived to 36 weeks PMA or discharge (whichever came first) and 609 infants returned for follow-up at 18-22 months corrected age. Only 535 infants had data available for the calculation of in-hospital growth velocity, at 36 weeks PMA or discharge, due to incomplete data collection for the rest

Comment [WC9]: How about data for the primary outcome? Did you have it in more babies?

(n = 146).

Characteristics of the Study Sample: The baseline characteristics of the lower and the higher saturation groups, including the anthropometric measures, were similar (TABLE 1). ~~The means for individual anthropometric measures (weight, length and head circumference), at different study time points, were not significantly different (not shown). The time from birth to initiate feeds and time to achieve full feeds were also similar between groups (TABLE 2). The mean 24-hour energy intake on the pre-specified study days was not different between groups and approximated 80kcal/kg/day on day 7, advancing progressively until 36 weeks postmenstrual age, to approximately 100kcal/kg/day. The macronutrient composition of energy source was also not different between groups (TABLE 2).~~

~~Primary Outcome (TABLE 3):~~ The rate of the composite primary outcome, weight < 10th percentile or death at 36 weeks PMA (or discharge if earlier) did not differ significantly between the lower saturation and the higher saturation groups (55.6 and 57.7% respectively; relative risk with lower oxygen saturation 0.95; 95% confidence interval [CI] 0.8 to 1.1, p = 0.43, TABLE 3). The percentage of infants with weight < 10th percentile and the growth velocity did not differ between the groups. The means for individual anthropometric measures (weight, length and head circumference), at different study time points, were not significantly different (not shown). The time from birth to initiate feeds and time to achieve full feeds were also similar between groups (TABLE 2). The mean 24-hour energy intake on the pre-specified study days was not different between groups and approximated 80kcal/kg/day on day 7, advancing progressively until 36 weeks postmenstrual age, to approximately 100kcal/kg/day. The macronutrient composition of energy source was also not different between groups (TABLE 2).

Comment [AD10]: Perhaps you need a table comparing the analysis sample to the rest of the missed babies to reassure readers that there were no systematically missing data.

Comment [AD11]: I would add a graph over time showing these growth trajectories by group.

Comment [WC12]: Agree. I think this is very important as otherwise the data would not be available. You could give raw data in a table and z scores in figures.

Comment [WC13]: I think we should relate growth velocity from birth to 36 weeks in relation to caloric intake. A figure may be the best.

Comment [AD14]: I would add a graph over time showing these growth trajectories by group.

Comment [WC15]: Agree. I think this is very important as otherwise the data would not be available. You could give raw data in a table and z scores in figures.

Comment [WC16]: Address when growth failure started. You may have to say the %of <10th percentile at each time of anthropometric measurements.

Although there was some catch-up growth, and the proportion with growth restriction decreased at the 18-22 months follow-up (35.4 and 31.3%, respectively), the composite outcome of weight < 10th percentile or death again was not different between groups (RR 1.1, 95% CI 0.9 to 1.4, p = 0.23). Similar results were observed when sub-group analysis was done by gestational age strata.

Comment [AD17]: I think this is the first time we see a mention of this composite outcome. You need to justify and mention this outcome at different time points in the Methods section. This also has implications for what your analysis sample (and your denominator) truly is (up until now and looking at fig 1, I was thinking that it was just survivors!).

Similarly, the percentage with length and head circumference < 10th percentile at 36 weeks PMA was also not different between groups (TABLE 4). Again, similarly to the weight outcome, at the 18-22 months follow-up the percentage of infants with length and head circumference <10th percentile was less than that seen at the 36 weeks PMA measure, although the amount of recovery or catch-up was less for length. In-hospital growth velocity to 236 weeks PMA was not different between the lower and the higher saturation groups (13.6 ± 2.4 vs. 13.4 ± 2.6 gm/kg/d, p = 0.69). The similarity in growth velocity between saturation groups was not influenced by gestational age strata (TABLE 3). The degree of growth restriction at 36 weeks PMA was more pronounced for length (z-score of -2.1) than for weight (-1.5) or head circumference (-1.1).

Similar to the findings in the main trial, the incidence of ROP in this sub-cohort was significantly lower in the lower saturation group (7 vs.17.8%, p = 0.0001). The other clinical outcomes, such as death before discharge and BPD (defined as use of supplemental oxygen at 36 weeks PMA), were not different between groups (TABLE 4).

Comment [WC18]: I would think this table is not needed

As was intended by the protocol, the median levels of oxygen saturation while on supplemental oxygen differed between randomization groups (FIGURE 2). The number of days on oxygen supplementation was also greater in the higher saturation group. However, as in the

main trial, there was a substantial overlap and the actual attained median levels of saturation were higher than the target levels.

When analysis was done by quartiles of the actual attained median saturations, infants with median saturations in the lowest quartile had higher risk for death or weight <10%ile at 36 weeks PMA when compared to the highest quartile (70.3 vs. 43.5%, RR 1.6, 95% CI 1.3-2.0, p = 0.0001). This was also seen at 18-22 months (51.6 vs. 18.8%, RR 2.6, 95% CI 1.9-3.6, p = 0.0001) (TABLE 5). When severity of illness was factored in, an increasing proportion of ill infants were seen when attained SpO2 decreased from highest to lowest quartile (14, 29, 44 and 51%, respectively; p <.0001).

Comment [AD19]: So how do these results comport with your main findings showing no differences? Would readers be left with a mixed and confusing message?

Comment [AD20]: Not clear what you mean; are the rates presented for illness severity or growth outcome?

Discussion:

In this large, multicenter, trial which randomly assigned, from birth, low gestational age premature infants to lower saturation or higher saturation targets while on supplemental oxygen, we found no difference in the primary outcome of death or weight less than 10th percentile (growth restriction) at 36 weeks PMA or at 18-22 months follow-up, by randomized group assignment. We also found no difference in the in-hospital growth velocity between the two groups. However, we did find that when actual attained median oxygen saturations were assessed, infants with median saturations in the lowest quartile had a higher risk for death or weight <10%ile when compared to the highest quartile , both at 36 weeks PMA and 18-22 months corrected age. Our outcomes differ from the observational and non-randomized study of Tin *et al*, who used two different saturation targets from birth by virtue of differing unit policies[18], and reported that infants cared for in the unit that maintained infants with lower~~higher~~ saturation targets were less~~more~~ likely to have growth restriction at discharge, as well as de~~in~~creased risk for ROP and BPD. Other studies of targeted oxygen saturation have not found a

difference in growth. Although saturation targeting in the BOOST trial[16] was started at 32 weeks PMA for infants still requiring oxygen supplementation, Askie *et al* found no difference in growth at 36 weeks PMA or at 12 months corrected age. Just recently, the similarly designed Canadian Oxygen Trial reported no difference in percentiles of all parameters of growth at 18 months follow-up[24]. The growth outcome from a meta-analysis of trials that randomize to differing saturations from birth is forthcoming [25, 26].

Consistent with other masked, randomized trials of targeting different oxygen saturation ranges [16, 17], the actual attained oxygen saturation levels have a tendency to overlap, presumably because of the dynamism of preterm infant oxygenation. The frequent episodes of desaturations in the majority of preterm infants require adjustments of the fraction of inspired oxygen (FiO2), and lead to wide fluctuations in SpO2[27]. In the absence of an automated FiO2 delivery system, or at least one-to-one dedicated nursing, underestimating or overestimating FiO2 delivery to keep infants tightly within target saturation ranges is difficult[28, 29]. Anticipating this limitation, comparison of the extreme quartiles of attained median oxygen saturations shows that spending more time in the lowest quartile (median saturation between 69-91%) is associated with increased risk for death or growth failure. Analysis of severity of illness (defined as FiO2 > 0.4 and mechanical ventilation for more than 8 hours in the first 15 days) according to quartile of actual median SpO2, showed that an increasing proportion of ill infants are seen with decreasing quartiles of attained SpO2. However, this may just be another indicator of increased disease severity.

Bronchopulmonary dysplasia is promoted by exposure to oxygen and mechanical ventilation, both variables that infants assigned to the higher saturation group were exposed to for longer periods. Unlike the main trial[19], wherein the rate of BPD (as defined by use of

supplemental oxygen at 36 weeks PMA) was higher in the infants in the higher oxygen saturation group, the difference in the rates for BPD using any definition (moderate or severe by consensus definition or by physiologic definition) did not reach significance in this subgroup. It has been described that preterm infants with morbidities such as BPD have poorer growth[30]. STOP-ROP and BOOST were trials that randomized infants to different saturation targets. Whilst starting a few weeks after birth, they both showed higher rates of pulmonary sequelae and/or BPD in the higher saturation group of infants but growth outcomes were unaffected[16, 17]. Our data does not help to resolve the question of whether the presence of BPD itself promotes the development of growth failure.

Comment [WC21]: I would delete all of this as this is a power issue, mostly.

Retinopathy of prematurity is another preterm infant morbidity that is associated with exposure to higher levels of oxygenation. The main trial indeed showed a substantial decrease in severe ROP in survivors who were kept in the lower target saturation range[19]. It has been noted that slow patterns of early weight gain can predict ROP in high risk infants[31, 32]. Insulin-like growth factor-1 (IGF-1) levels are described to be deficient at preterm birth and further reduced by conditions that preterm infants experience (e.g. poor nutrition, acidosis, and sepsis). This deficiency of IGF-1 has been associated with less vessel growth, greater retinal hypoxia and elevation of hypoxia-induced vasoproliferative factors (e.g. vascular endothelial growth factor) and more severe ROP[33]. In the present study, despite the difference in severe ROP between groups, a similar difference in growth velocities or weight was not seen at any of the time points studied.

This subgroup of the SUPPORT trial also showed the previously reported increase (although not significant) in mortality in the lower saturation group. When analysis was done by quartiles of the actually attained median oxygen saturation, irrespective of assignment group,

there was a higher risk for death in the lowermost quartile when compared to the uppermost quartile. We speculate that the infants whose actual median saturations were in the lower quartiles were more ill and therefore experiencing more episodes of desaturation[34].

Intermittent determinations of 24-hour nutritional intake ('snapshots') showed that the caloric intake and intake composition was similar between the lower and the higher saturation groups. However, the entire population suffered from sub-optimal intake. Although the earliest time point for collection of nutritional information was age 7 days, the protein intake at this time only translated into about 3.2 grams/kg/d in either group. The importance of improved early protein intake and the association with better growth outcomes is achieving greater recognition[7]. The generally recommended energy intake for healthy low birth weight infants of 90-120kcal/kg/d [35] was only marginally achieved , even by 36 weeks PMA. Calorie distribution according to macronutrient composition varied over time, but swung from predominantly lipid to predominantly carbohydrate over time; on day 7, there was a predominance of calories from lipid intake (47% lipid, 38% carbohydrate, 15% protein) and by 36 weeks PMA, there was a predominance of calories from the carbohydrate fraction (55% carbohydrate, 35% lipid, 10% protein). This macronutrient distribution is very different from the nutrient supplies that normally growing fetuses receive (high fraction of amino acids with just enough lipid and glucose)[36]. While some of the limitations to intake relate directly to a baby's clinical condition, it has been shown that the clinician's perception of illness may still limit provision of optimal nutritional intakes[37]. The shortfall in nutritional intake can translate into profound cumulative nutritional intake deficits that may account for the significant rates of growth restriction in this population (46-50%). The rate of growth restriction in the present study appears to be less when compared to older studies, but caution is needed in interpretation as the reference growth curves

Comment [WC22]: This should be highlighted in the Results section

used in this study under-estimate measures as compared to the older utilized growth curves[21]. The updated intrauterine growth curves represent a contemporary, large, racially diverse US cohort. Compared to the older widely-used, Lubchenco growth curves, these curves are slightly shifted rightward especially at the higher gestational ages. The use of fetal growth reference standards as the ideal for postnatal growth may be another limitation of this study. *In utero* conditions for the fetus are completely different to the extra-uterine environment and the metabolic demands on an infant born prematurely. Comparison between the growth of an infant born preterm and a fetus of the same gestational age places the preterm infant at a great disadvantage, hence the inevitable "excessive" incidence of postnatal growth restriction. Plotting the actual post-natal growth measures of a recent cohort of VLBW infants (including early physiologic weight loss) against fetal growth curves showed that they were consistently below the 10%ile by 36 weeks or discharge[30].

The strength of our data lie in the large group of preterm infants studied and randomized from birth to two target saturation ranges within the accepted limits at the time. Although the nutritional dataset is limited and we are unable to measure cumulative deficits, the intermittent measures of nutritional intake demonstrate the consistently inadequate provision of protein and non-protein caloric intakes.

Conclusion:

Oxygen saturation targeting from birth had no impact on growth outcomes~~, by group~~. However, when evaluated against actually attained values, the greatest degree of growth restriction was seen in babies with the lowest attained median oxygen saturation levels. The high

incidence of postnatal growth restriction persists despite use of an updated growth reference standard, and insufficient caloric provision remains an issue.

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Figure 1. Patient Distribution

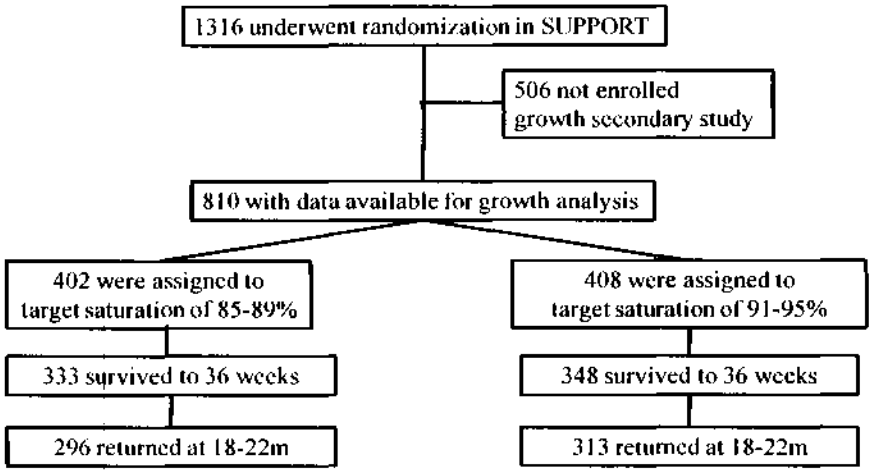

Table 1: Baseline Population characteristics

Characteristic[1]	Lower Saturation n=402	Higher Saturation n=408	p-value[2]
Gestational age, weeks	26.2 (1.1)	26.2 (1.1)	0.65
Birth weight, g.	838.6 (186)	839.9 (191)	0.87
Birth weight < 10th %ile[3] (SGA)	40/402 (10.0)	53/408 (13.0)	0.19
HC at birth	23.5 (1.8)	23.6 (1.9)	0.74
HC at birth < 10th %ile[3]	41/396 (10.4)	53/398 (13.3)	0.19
Length at birth	33.4 (2.9)	33.3 (2.9)	0.22
Length at birth <10th %ile[3]	50/396 (12.6)	57/400 (14.3)	0.48
Non-Hispanic black	179/402 (44.5)	159/408 (39.0)	0.10
Multiple birth	90/402 (22.4)	112/408 (27.5)	0.14
Antenatal steroids	390/402 (97.0)	389/407 (95.6)	0.29
Vaginal delivery	138/402 (34.3)	147/408 (36.0)	0.56
Mother's education: HS grad	69/311 (22.2)	90/313 (28.8)	0.07
% Male	211/402 (52.5)	236/408 (57.8)	0.19

[1]presented as mean (SD) for continuous variables, n/N (%) Yes for categorical variables.
[2]adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center, using linear mixed models for continuous variables and robust Poisson regression for categorical variables, where appropriate
[3]based on 10th percentile weight for GA, by gender, from Olsen growth tables.

Table 2. Nutritional Intake

Combined parenteral and enteral intake (Kcal/kg/day):	Lower	Higher	

	Saturation n=402	Saturation n=408	p-value[2]
Total energy:			
Day 7	84.2 (25.0)	81.8 (22.4)	0.24
Day 14	91.8 (26.1)	90.3 (24.9)	0.57
Day 21	93.8 (37.8)	92.8 (27.54)	0.72
Day 28	97.2 (29.1)	95.6 (29.3)	0.62
32 weeks PMA	104.3 (29.8)	105.2 (27.3)	0.90
36 weeks PMA	110.5(36.4)	108.1 (33.5)	0.47
Discharge or 36 weeks PMA	106.4 (40.5)	100.8 (34.0)	0.83
Protein:			
Day 7	13.2 (3.2)	13.0 (3.3)	0.66
Day 14	12.5 (4.8)	12.1 (4.8)	0.46
Day 21	10.7 (5.3)	10.9 (5.0)	0.60
Day 28	9.9 (5.0)	10.4 (4.9)	0.31
32 weeks PMA	10.0 (5.3)	9.9 (4.9)	0.80
36 weeks PMA	10.5 (5.0)	10.4 (4.9)	0.96
Discharge or 36 weeks PMA	10.7 (5.3)	10.1 (4.3)	0.72
Lipid:			
Day 7	40.4 (14.2)	39.0 (11.8)	0.24
Day 14	39.3 (14.7)	38.7 (12.2)	0.47
Day 21	38.7 (16.5)	38.3 (12.5)	0.48
Day 28	38.8 (12.9)	37.6 (12.2)	0.18
32 weeks PMA	37.8 (12.0)	38.4 (11.5)	0.83
36 weeks PMA	38.4 (11.9)	37.8 (11.9)	0.62
Discharge or 36 weeks PMA	37.3 (12.8)	34.3 (10.8)	0.67
Carbohydrate:			
Day 7	32.9 (15.8)	31.3 (15.3)	0.24
Day 14	43.8 (20.2)	43.5 (20.7)	0.98
Day 21	50.2 (27.0)	49.4 (22.2)	0.93
Day 28	53.7 (22.9)	52.0 (21.9)	0.53
32 weeks PMA	59.1 (20.3)	57.9 (20.3)	0.66
36 weeks PMA	60.8 (20.4)	60.1 (19.9)	0.83
Discharge or 36 weeks PMA	65.8 (23.3)	58.3 (19.4)	0.63
Age at first enteral feed (days) n, median, IQR	373, 4 (3-7)	380, 4 (3-7.5)	0.38
Age at first full enteral feed (days) n, median, IQR	337, 23(16-34)	345, 24 (16-34)	0.76

[1]presented as mean (SD) for continuous variables, except where noted.
[2]adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center, using linear mixed models for continuous variables; unadjusted rank sum test for age at first enteral feed and age at first full enteral feed

Table 3: Primary Outcomes

Outcome[1]	Lower Saturation N=402	Higher Saturation N=408	p-value[2]
All infants			
36 weeks PMA[3]:			
Death or wt < 10th %ile	223/401 (55.6)	232/402 (57.7)	0.43
Wt < 10th %ile	155/333 (46.6)	172/342 (50.3)	0.30
Growth velocity (g/kg/d)[4]	13.6 (2.4), 260	13.4 (2.6), 275	0.69
18-22 months FU:			
Death or wt < 10th %ile	136/384 (35.4)	122/390 (31.3)	0.22
Wt < 10th %ile	48/296 (16.2)	45/313 (14.4)	0.49
GA 24-25 weeks	Lower Saturation N=182	Higher Saturation N=174	
36 weeks PMA[3]:			
Death or wt < 10th %ile	122/182 (67.0)	124/172 (72.1)	0.31
Wt < 10th %ile	71/131 (54.2)	85/133 (63.9)	0.17
Growth velocity (g/kg/d)[4]	13.9 (2.1), 98	13.1 (2.8), 110	0.29
18-22 months FU:			
Death or wt < 10th %ile	87/175 (49.7)	78/170 (45.9)	0.55
Wt < 10th %ile	24/112 (21.4)	29/121 (24.0)	0.48
GA 26-27 weeks	Lower Saturation N=220	Higher Saturation N=234	
36 weeks PMA[3]:			
Death or wt < 10th %ile	101/219 (46.1)	108/280 (47.0)	0.65
Wt < 10th %ile	84/202 (41.6)	87/209 (41.6)	0.76
Growth velocity (g/kg/d)[4]	13.4 (2.6), 162	13.6 (2.5), 165	0.55
18-22 months FU:			
Death or wt < 10th %ile	49/209 (23.4)	44/220 (20.0)	0.30
Wt < 10th %ile	24/184 (13.0)	16/192 (8.3)	0.12

[1] presented as n/N (%) Yes; 36 week outcomes based on Olsen growth tables; follow-up outcomes based on WHO growth tables[17].

[2] p-values are from robust Poisson regression models and linear mixed models(growth velocity); adjusted for multiple birth clustering, SUPPORT stratification variables center, and gestational age group (models for 'All infants') and multiple birth clustering and center (models for GA subgroups);

** indicates statistical significance (p< .05)

[3] include infants discharged prior to 36 weeks PMA.

[4] calculated for the subset of survivors to 36 weeks PMA or discharge/transfer, whichever came first using the exponential method (Patel 2005, 2009) with available growth study data at Day 1 & 36 weeks : presented as mean (SD), n.

Table 4. Clinical and other Anthropometric Outcomes

	Lower Saturation	Higher Saturation	

Characteristic[1]	n=402	n=408	p-value[2]
Death by 36 weeks PMA	69 (17.2)	60 (14.7)	0.39
BPD, oxygen at 36 weeks PMA	132/333 (39.6)	158/348 (45.4)	0.08
Postnatal steroids for BPD	33/394 (8.4)	39/399 (9.8)	0.39
# days on ventilator[3], n, median, mean(SD)	n=329 9,21.0 (25.6)	n=344 14.5,22.7 (24.7)	0.17
# days supplemental oxygen[3], n, median, mean(SD)	n=329 47,53.1 (37.6)	n=344 60,60.6 (36.6)	0.0094**
Median SpO2 while on supp. oxygen, n, median (IQR)	382, 92 (91 to 94)	389, 94 (93 to 95)	<.0001**
Severe IVH	58/391 (14.8)	60/396 (15.2)	0.85
PVL	16/392 (4.1)	20/397 (5.0)	0.57
NEC	51/397 (12.9)	48/404 (11.9)	0.65
Late onset sepsis	144/397 (36.3)	139/404 (34.4)	0.70
PDA	181/397 (45.6)	200/403 (49.6)	0.27
Severe ROP	21/302 (7%)	56/314 (17.8%)	.0001**
n /N(%) with L <10th %ile at 36wk PMA	203/314 (64.7)	218/315 (69.2)	0.21
n /N(%) with L <10th ile at 18-22m	79/296 (26.7)	98/313 (31.3)	0.28
n /N(%) with HC <10th %ile at 36wk PMA	124/319 (38.9)	130/325 (40.0)	0.87
n /N(%) with HC <10th ile at 18-22m	46/296 (15.5)	49/313 (15.7)	0.92

[1]presented as mean (SD) for continuous variables, n/N (%) Yes for categorical variables, except where noted.
[2]adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center, using linear mixed models for continuous variables and robust Poisson regression for categorical variables, where appropriate, unadjusted rank sum test for days on ventilator and median SpO2
**indicates statistical significance (p<.05)
[3]subset of survivors to discharge, transfer, or 120 days, whichever came first

Figure 2. Distribution of Actual Median Saturation while on Supplemental Oxygen

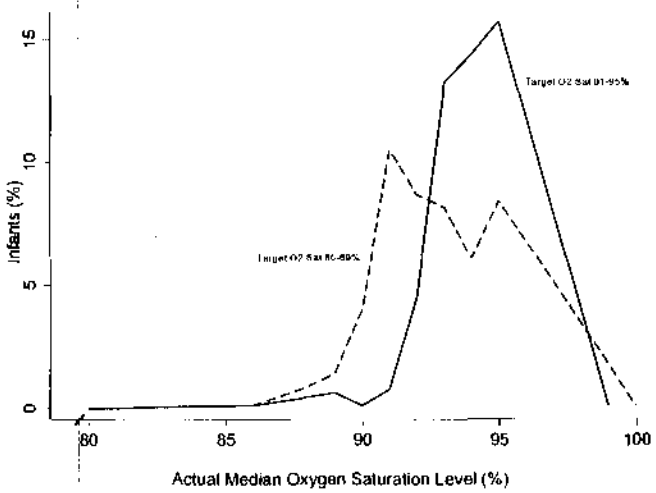

Table 5: Primary outcomes by actual median O2 saturation quartile[1]

Outcome[1] All infants	Quartile 1 n=158	Quartile 2 n=267	Quartile 3 n=158	Quartile 4 n=188	RR Q1 vs. Q4 (95% CI)	p-value[2]
36 weeks PMA[3]:						
Death	52/158 (32.9)	37/267 (13.9)	16/158 (10.1)	12/188 (6.4)	5.0 (2.8-8.9)	<.0001**
Death or wt < 10th %ile	111/158 (70.3)	162/267 (60.7)	78/155 (50.3)	81/185 (43.8)	1.6 (1.3-2.0)	<.0001**
Wt < 10th %ile	60/107 (56.1)	125/230 (54.4)	62/139 (44.6)	69/173 (39.9)	1.4 (1.1-1.8)	.0060**
18-22 months FU:						
Death	63/157 (40.1)	52/256 (20.3)	21/146 (14.4)	16/178 (9.0)	4.3 (2.7-7.1)	<.0001**
Death or wt < 10th %ile	81/157 (51.6)	90/256 (35.2)	38/146 (26.0)	32/178 (18.0)	2.7 (2.0-3.8)	<.0001**
Wt < 10th %ile	18/94 (19.2)	38/204 (18.6)	17/125 (13.6)	16/162 (9.9)	1.9 (1.0-3.4)	.0366**

[1]Outcomes presented as n/N(%), and Relative Risk (RR)
[2]adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center using robust Poisson regression.
**indicates statistical significance (p<.05)

From: Das, Abhik
To: Kristi Watterberg; Satyan Lakshminrusimha; kurt.schibler@cchmc.org; Bill Truog; RAP32@columbia.edu; mcw3@cwru.edu; bpoindex@iu.edu; vanmeurs@leland.stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]; goldb008@mc.duke.edu; sshankar@med.wayne.edu; Uday Devaskar; Leif Nelin; [SCRN] Stoll, Barbara; M.D. Wally Carlo; Wallace, Dennis; Gantz, Marie; Edward Bell; Anne Marie Reynolds; Barbara Schmidt; Carl D"Angio; Kathleen.A.Kennedy@uth.tmc.edu; Pablo.Sanchez@UTSouthwestern.edu; alaptook@WIHRI.org
Cc: Ivan.Frantz@childrens.harvard.edu; Roger.Faix@hsc.utah.edu; SDuara@med.miami.edu; Neil Finer; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu; EMcGowan@tufts-nemc.org
Subject: RE: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Tuesday, July 16, 2013 1:12:48 PM

Yeah, I am blaming my Indian English for that! I already changed it to 'specified' at Michele's suggestion, but 'delineated' works as well!

Thanks

Abhik

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Tuesday, July 16, 2013 1:10 PM
To: Satyan Lakshminrusimha; kurt.schibler@cchmc.org; Bill Truog; RAP32@columbia.edu; mcw3@cwru.edu; bpoindex@iu.edu; vanmeurs@leland.stanford.edu; Rosemary (NIH/NICHD) [E] Higgins; goldb008@mc.duke.edu; sshankar@med.wayne.edu; Uday Devaskar; Leif Nelin; [SCRN] Stoll, Barbara; M.D. Wally Carlo; Das, Abhik; Wallace, Dennis; Gantz, Marie; Edward Bell; Anne Marie Reynolds; Barbara Schmidt; Carl D'Angio; Kathleen.A.Kennedy@uth.tmc.edu; Pablo.Sanchez@UTSouthwestern.edu; alaptook@WIHRI.org
Cc: Ivan.Frantz@childrens.harvard.edu; Roger.Faix@hsc.utah.edu; SDuara@med.miami.edu; Neil Finer; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
Subject: Re: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

This looks like a fine letter to me. Perhaps one word - "enshrined" (point #2, first sentence) might be changed to something less reverential, such as "delineated"?

Kristi

>>> "Das, Abhik" <adas@rti.org> 7/15/2013 11:32 AM >>>
Hello All:

At its previous monthly call, the steering committee wanted us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have written the attached draft response that has been vetted by the legal folks at RTI. Neil, Wally and Rose have also looked at this text. Please take a look and let me know your feedback by July 22. We can then finalize and send the response.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe

Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, July 16, 2013 11:20 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]; Shapiro, Neil (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Question about QFR - NIH concerns about response to senate

FYI

I will keep you updated on what I learn.

(b)(5)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, July 16, 2013 11:16 PM
To: Cochran, Norris (HHS/ASFR)
Subject: Question about QFR - NIH concerns about response to senate

Norris,

Given we did not connect tonight, let me pose my question by email.

This morning we received from a third party a copy of a QFR to the Senate from HHS in follow up to KGS hearing earlier this year. Could you please help me understand the review process for QFRs in HHS? I do not believe that NIH was asked to review or was provided a copy FYI of this QFR.

As you may be aware, there was (b)(5)
(b)(5)

This qfr seems to be (b)(5)

Can you help me out? Also, can you tell me when the qfrs were actually delivered to the senate?

Thanks Norris.

kathy

SUPPORT Clinical Trial
The University of Alabama at Birmingham (UAB) recently received a letter from the Office for Human Research Protections (OHRP) about the SUPPORT clinical trial, a research study of premature infants and supplemental oxygen. In the letter, OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study.

1. Could you please provide the specific scientific data that existed at the start of the study that shows this increased risk?

Response:

At the time the SUPPORT study began, substantial information was available on possible risks of increased mortality at lower oxygen levels. In 2003, an international group of over 30 experts began a collaboration around improving the understanding of neonatal oxygenation through well-designed clinical trials. One output of this nascent collaboration was a 2003 commentary in Pediatrics (Cole et al., Resolving Our Uncertainty About Oxygen Therapy, Pediatrics 2003;112:1415), which discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." This information, and other similar concerns, is more fully described in the letter dated June 4, 2013, from OHRP to the University of Alabama, which can be found on OHRP's web site at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf.

2. If no such data existed, could you please explain why it would be scientifically credible or ethical to explain unknown risks of a study?

Response:
At the time the SUPPORT study began, substantial information was available on possible risks of increased mortality at lower oxygen levels.

3. What is the process for appealing the findings of OHRP? Is there a mechanism for having an independent review of OHRP actions especially when they are so universally called into question as in this case? (Please see, for example, editorials and correspondence in the New England Journal of Medicine and The Hastings Center Bioethics Forum).

Response:
OHRP's compliance oversight procedures state that an institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation, http://www.hhs.gov/ohrp/compliance/evaluation/index.html. OHRP has no recollection of any such requests for reconsideration from an institution against which OHRP made a determination of noncompliance. Historically, OHRP has received such requests only from complainants concerned that OHRP did not agree with their allegations of noncompliance. If such complainants are unsatisfied with the response of the OHRP Director, OHRP informs them that they may communicate with the Principal Deputy Assistant Secretary for Health and the Assistant Secretary for Health and ask them to review the matter.

Laura Friedel
Committee on Appropriations
Subcommittee on Labor, HHS and Education
156 Dirksen Senate Office Building
Washington, DC 20510
202-224-0314

From: Das, Abhik
To: EMcGowan@tufts-nemc.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Tuesday, July 16, 2013 9:56:56 AM
Attachments: 130607_Letter to SUPPORT Study Investigators Requesting Study Data_FINAL_Signed.doc
Carome response v1.docx

Dr. McGowan:

Sorry to have missed you in the initial email. Please let me know if you have any comments.

Thanks

Abhik

From: Das, Abhik
Sent: Monday, July 15, 2013 1:33 PM
To: '[SCRN] Stoll, Barbara (barbara_stoll@oz.ped.emory.edu)'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Anne Marie Reynolds'; 'Barbara Schmidt'; 'Bell, Edward'; 'Bill Truog'; 'Brenda Poindexter (bpoindex@iu.edu)'; 'Carl D'Angio'; 'Das, Abhik (adas@rti.org)'; 'Gantz, Marie (mgantz@rti.org)'; 'goldb008@mc.duke.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'Leif Nelin'; 'mcw3@cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'RAP32@columbia.edu'; 'Satyan Lakshminrusimha'; 'sshankar@med.wayne.edu'; 'Uday Devaskar'; 'vanmeurs@leland.stanford.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'
Cc: Finer, Neil; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Ivan Frantz (Ivan.Frantz@childrens.harvard.edu) (Ivan.Frantz@childrens.harvard.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Importance: High

Hello All:

At its previous monthly call, the steering committee wanted us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have written the attached draft response that has been vetted by the legal folks at RTI. Neil, Wally and Rose have also looked at this text. Please take a look and let me know your feedback by July 22. We can then finalize and send the response.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
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web: www.citizen.org

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June 7, 2013

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
3040 East Cornwallis Road
Post Office Box 12194
Research Triangle Park, NC 27709-2194

Waldemar A. Carlo, M.D.
Director, Division of Neonatology
University of Alabama at Birmingham
Women & Infants Center
1700 6th Avenue
South Birmingham, AL 35233

Neil N. Finer, M.D.
Chief, Division of Neonatology
Department of Pediatrics
School of Medicine
University of California, San Diego
3020 Children's Way, MC 5109
San Diego, CA 92123-5109

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Drs. Das, Carlo, and Finer:

In accordance with the National Institutes of Health's (NIH's) long-standing data sharing policy,[1] which requires data sharing for all NIH-funded grants, Public Citizen's Health Research Group respectfully requests a digital copy of all individual subject-level data — without subject identifiers — obtained for the SUPPORT study that was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The data being requested includes the data on actual oxygen saturation levels that were achieved for each subject over the course of their involvement in the study. We are seeking all data for (a) the 1,316 subjects enrolled and randomly assigned to one of the four experimental groups in the SUPPORT study; and (b) those subjects who were eligible to be, but were not, enrolled in the SUPPORT study, and for whom

[1] National Institutes of Health. NIH Data Sharing Policy and Implementation Guidance. March 5, 2003. http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. Accessed June 6, 2013.

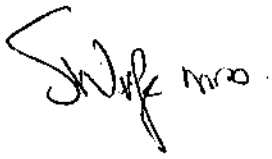
data was collected and published regarding demographics, baseline clinical characteristics, and clinical outcomes.[2]

We also respectfully request that you provide with the data (a) an explanation of the format used for storing the data; (b) a description of how the data was coded; and (c) the case report forms for each subject.

Thank you for your prompt attention to this request. Please notify us immediately if you have any questions about the data we are seeking or anticipate problems fulfilling our request.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Senior Advisor and Founder
Public Citizen's Health Research Group

cc: Dr. Allan Guttmacher, Director, National Institute of Child Health and Human Development

[2] Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics.* March 2012;129(3):480-484.

July 8, 2013

Michael A. Carome, M.D.
Director, Public Citizen's Health Research Group
Washington, DC.

Dear Sir:

In reference to your letter dated June 7, 2013, and on behalf of the NICHD Neonatal Research Network (NRN) Steering Committee, we are currently unable to entertain your request for access to data collected for the NRN Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). The principal reasons behind this decision are as follows:

1. As mentioned in the clinicaltrials.gov citation for this trial, extended follow-up at school age for a cohort of children enrolled in SUPPORT is still ongoing. Thus, in accordance with the NIH guidance referenced in your letter, we have no plans to share the data from this study before the follow up portion of the study is complete and the final results have been published in a peer reviewed journal.
2. The following policies enshrined in the Network's Policies and Procedures charter guide the NRN in responding to requests from external scientific investigators:
   "From time-to-time, the NRN receives requests from non-Network researchers for protocol documents (protocol, manual, and forms) and study data for pre-specified purposes. All requests should be sent to the NICHD Program Scientist for consideration. Generally, data are not released until two years following publication of a primary study.
   Depending on the nature of the request, it may go to the Data Access Subcommittee or directly to the Steering Committee. The Steering Committee votes to approve release of the requested information. The external requestor is asked to acknowledge the use of the NICHD Neonatal Research Network materials in all relevant applications, presentations, and publications."
   Typically, the Steering Committee requires a scientific protocol with stated hypotheses, specific aims, background and significance and a reasonably detailed study design and analysis plan, as well as a budget to entertain such external requests.
3. As per the data sharing plan proposed by the NRN Data Coordinating Center (DCC) and approved by NIH, if external data sharing is approved by the NRN Steering Committee and NICHD, the DCC will create de-identified limited-access data sets for this purpose. Although the data sets will be stripped of identifiers and otherwise modified to prevent easy identification of patients in the study, the narrow focus of the population to be analyzed and the possible rarity of some outcome measures and risk factors might make it possible for an identification to be made. Therefore, in order to protect the confidentiality and privacy of the subjects, external investigators granted access to these data must adhere to strict requirements defined by the NRN Steering Committee that are incorporated into a standard Data Distribution Agreement to which all external investigators seeking the data must agree to abide and adhere to. The Data

Distribution Agreement may be subject to review by the legal departments and IRBs of the DCC and the NRN clinical centers, and must be approved by the Steering Committee. Finally, in accordance with NICHD policies, outside researchers will be required to submit an approval from their IRB.

In summary, in accordance with NIH approved policies, we will not be presently releasing the requested data from the SUPPORT trial. Once the extended follow up for the SUPPORT trial concludes and its primary results are published, the NRN will be happy to entertain scientifically rigorous protocols that seek access to the trial data to conduct secondary analyses that may contribute to the science of neonatology. Such requests will need to follow established data sharing policies adopted by the NRN and NIH and adhere to required human subjects protections, as referred to earlier in this letter.

Please let us know if there are any questions.

Sincerely

Abhik Das

Waldemar Carlo

Neil Finer

for the NICHD Neonatal Research Network Steering Committee

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Pun Med Central
Date: Monday, July 15, 2013 5:25:21 PM

Thanks. Will do.

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 15, 2013 2:25 PM
To: Vaucher, Yvonne; Rich, Wade; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Pun Med Central

You need to submit as the first author –
Stephanie can send you the instructions.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Monday, July 15, 2013 5:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Pun Med Central

Rose,
We have not submitted it and Wade does not recall submitting any of our papers to Pub Med Central himself. He thought that someone central/?Stephanie Archer submitted them.
Happy to do whatever we need to do but need instructions.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 12, 2013 11:48 AM
To: Vaucher, Yvonne; Rich, Wade; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Pun Med Central

Hi
Did the SUPPORT 18 month outcome paper get submitted to Pub Med Central? Please send us the NIHMS #.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Das, Abhik
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Monday, July 15, 2013 1:30:48 PM

Yes
Include the support investigators

Sent from my iPhone

On Jul 15, 2013, at 12:46 PM, "Das, Abhik" <adas@rti.org> wrote:

> Rose:
>
> I am getting ready to send this to the steering committee, but should I also send it to the then steering committee members (Richard, Roger, Ivan, Shahnaz and Mike)?
>
> Thanks
>
> Abhik
>
> **From:** Waldemar Carlo [mailto:wcarlo2@gmail.com]
> **Sent:** Monday, July 15, 2013 12:43 PM
> **To:** Das, Abhik
> **Subject:** Re: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
>
> Abhik.
>
> I have read the letter and agree. Sorry for the delay.
>
> On Jul 9, 2013 9:51 AM, "Das, Abhik" <adas@rti.org> wrote:
> Wally and Neil:
>
> The steering committee wants us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have formulated the attached draft response that has been vetted by the legal folks at RTI. Please take a look and send me any changes. Once we agree on the draft, I will send on to the steering committee for their concurrence.
>
> Thanks
>
> Abhik
>
> **From:** Michael Carome [mailto:mcarome@citizen.org]
> **Sent:** Friday, June 07, 2013 5:16 PM
> **To:** Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
> **Cc:** Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe

Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

From: Stevens, Timothy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756
Date: Saturday, July 13, 2013 7:57:05 AM

Hi Rose

I shared the comments from Pediatrics with my coauthors in my reply to the reviewers that circulated with the revised manuscript.

I've now incorporated the comments from my coauthors into the revised manuscript.

Is there anything else before I submit?

Thanks

Tim

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, July 12, 2013 11:03 PM
To: Stevens, Timothy
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756

Nice work Tim
If you need any help with this let me know Thanks for seeing this study through and congratulations Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 12, 2013 5:46 AM
To: Wally Carlo, M.D.; Finer, Neil
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756

Here were the comments from Pediatrics for the breathing outcomes paper - I thought Tim had shared them with the co-authors.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Tuesday, April 30, 2013 1:04 PM

To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756

Hi Rose

Here is the decision from Pediatrics about the Breathing Outcomes manuscript. Most of the comments are easily addressed. The two toughest are from the editor, does each coauthor meet authorship criteria and please address the "ethical concerns" of SUPPORT.

I'll draft a revised manuscript that responds to the reviewers concerns.

I'd appreciate your thoughts.

Thanks

Tim

-----Original Message-----
From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com [mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of PediatricsEditorial@aap.org
Sent: Tuesday, April 30, 2013 9:59 AM
To: Stevens, Timothy
Subject: PEDIATRICS: Decision Letter - MS# 2013-0756

30-Apr-2013

RE: MS# 2013-0756

Title: Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

Authors: Stevens, Timothy; Finer, Neil; Carlo, Waldemar; Szilagyi, Peter; Phelps, Dale; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Newman, Jamie; Das, Abhik; Do, Barbara; Schibler, Kurt; Rich, Wade; Newman, Nancy; Ehrenkranz, Richard; Peralta-Carcelen, Myriam; Vohr, Betty R.; Wilson-Costello, Deanne; Yolton, Kimberly; Heyne, Roy; Dusick, Anna; Evans, Patricia; Vaucher, Yvonne; Adams-Chapman, Ira; McGowan, Elisabeth; Bodnar, Anna; Pappas, Athina; Hintz, Susan; Acarregui, Michael; Fuller, Janell; Goldstein, Rikki; Bauer, Charles; O'Shea, Thomas; Myers, Gary; Higgins, Rosemary

Dear Dr. Stevens:

The editors of Pediatrics feel that your manuscript may have merit but would require substantial work before it could be seriously considered for publication. You are welcome to submit a revised manuscript, which will be sent out for peer review; referees may include past and new reviewers. Please be aware that fewer than half of such papers are ultimately accepted.

If you decide to resubmit this manuscript, you must address the concerns of the reviewers at the end of this e-mail. Your successful response to the critiques of the current reviewers does not guarantee acceptance of the manuscript, because new reviewers may be added for the revised paper and may have different concerns.

In addition to the reviewers' comments below, please address the following items from the editors:

1) It appears that not all the coauthors listed meet the authorship criteria.

2) Please address the ethical concerns about the original study.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewers and the editors in the space provided under "Author's Response." You can use this space to document any additional changes you make to the original manuscript. In addressing any substantive suggestions or criticisms made by our reviewers, please make a numerical listing of what you have done, or not done, in regard to each suggestion of the reviewers. If the reviewer's request is for clarification, please make the clarification in the text of the paper. Remember that explaining what you mean to the editors and reviewers does not help the reader.

Your revision should be submitted via http://mc.manuscriptcentral.com/pediatrics. In your "Author Center," click on "Manuscripts with Decisions." In the "Actions" box, click on "Create a Revision." Please upload the revised version of your manuscript and delete the older version from the system before completing the submission. The revised manuscript should have no editing tags; it should be an unmarked version without margin notes or boldface notes. Once submitted, your revised manuscript's number will be appended to denote a particular revision (R1, R2, etc).

If you choose to do so, a revised manuscript must be submitted within 90 (ninety) days of this date. You can monitor the time remaining through your Author Center.

For additional requirements, see the attached document.

Sincerely,

Lewis R. First, MD
Editor-in-Chief, Pediatrics
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics, Vermont Children's Hospital at Fletcher Allen Health Care
802-656-0027 (office)
802-656-2077 (fax)
lewis.first@uvm.edu

Reviewer: 1

(b)(4),(b)(6)

Page 0140 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 0142 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Stevens, Timothy
Subject: RE: PEDIATRICS: Decision Letter - MS# 2013-0756
Date: Friday, July 12, 2013 3:57:49 PM

This is a very positive review and an opportunity to make the paper better and address positively the controversy.

Way to go, Tim!!! A very high impact factor.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

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Sent: Friday, July 12, 2013 7:46 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756

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Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
6100 Executive Blvd., Room 4B03
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For overnight delivery use Rockville, MD 20852
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higginsr@mail.nih.gov

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To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756

Hi Rose

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Thanks

Tim

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From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com [mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of PediatricsEditorial@aap.org
Sent: Tuesday, April 30, 2013 9:59 AM
To: Stevens, Timothy
Subject: PEDIATRICS: Decision Letter - MS# 2013-0756

30-Apr-2013

RE: MS# 2013-0756

Title: Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

Authors: Stevens, Timothy; Finer, Neil; Carlo, Waldemar; Szilagyi, Peter; Phelps, Dale; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Newman, Jamie; Das, Abhik; Do, Barbara; Schibler, Kurt; Rich, Wade; Newman, Nancy; Ehrenkranz, Richard; Peralta-Carcelen, Myriam; Vohr, Betty R.; Wilson-Costello, Deanne; Yolton, Kimberly; Heyne, Roy; Dusick, Anna; Evans, Patricia; Vaucher, Yvonne; Adams-Chapman, Ira; McGowan, Elisabeth; Bodnar, Anna; Pappas, Athina; Hintz, Susan; Acarregui, Michael; Fuller, Janell; Goldstein, Rikki; Bauer, Charles; O'Shea, Thomas; Myers, Gary; Higgins, Rosemary

Dear Dr. Stevens:

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If you decide to resubmit this manuscript, you must address the concerns of the reviewers at the end of this e-mail. Your successful response to the critiques of the current reviewers does not guarantee acceptance of the manuscript, because new reviewers may be added for the revised paper and may have different concerns.

In addition to the reviewers' comments below, please address the following items from the editors:

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewers and the editors in the space provided under "Author's Response." You can use this space to document any additional changes you make to the original manuscript. In addressing any substantive suggestions or criticisms made by our

reviewers, please make a numerical listing of what you have done, or not done, in regard to each suggestion of the reviewers. If the reviewer's request is for clarification, please make the clarification in the text of the paper. Remember that explaining what you mean to the editors and reviewers does not help the reader.

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If you choose to do so, a revised manuscript must be submitted within 90 (ninety) days of this date. You can monitor the time remaining through your Author Center.

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Sincerely,

Lewis R. First, MD
Editor-in-Chief, Pediatrics
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics, Vermont Children's Hospital at Fletcher Allen Health Care
802-656-0027 (office)
802-656-2077 (fax)
lewis.first@uvm.edu

Reviewer: 1

(b)(4),(b)(6)

Page 0146 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 0147 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 0148 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

From: Kennedy, Kathleen A
To: Phelps, Dale
Cc: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Secondary Final Revision
Date: Friday, July 12, 2013 12:39:55 PM
Attachments: ROP Natural History Study Manuscript (final revision for J Perinatol).doc

It turns out that there isn't a "discrepancy" with the primary SUPPORT paper to explain based on the data error. The numbers on this paper are different from what was reported in the main paper because we're using severe ROP or death (whenever reported) and the primary paper reported severe ROP (whenever reported) or death before discharge. We could try to explain this in the Methods or in a footnote but I think it might cause more rather than less confusion. This manuscript is really about timing of ROP not the competing outcome of death. Cochrane reviewers will likely go to the primary manuscript; I doubt they will look at this one. If you try to look at both papers, and you look at the flow diagram for each, it's clear that there are many differences in the way to population was accounted for because the study purposes were different. There are many other differences besides the 1 infant with the error in ROP coding. The main paper divides them by CPAP arm. We mention 2 withdrawals that I don't see mentioned in the main paper (maybe we used their GDB outcomes in the main paper). I don't see any numbers that are going to raise a red flag because they're reporting the same thing and have different numbers.

I've sent Wally an email about the error we uncovered. I think it's up to him and the SUPPORT subcommittee if they want to pursue it further. It doesn't sound like he thinks anything else is warranted. There's also the separate issue of trying to make sure that we avoid something similar with Inositol.

Rose was fine with the author order. On this particular topic, she thought it was appropriate for you to be the senior author.

Yes, Lisa has updated all the tables and figures and I've updated the numbers in the text as needed for the infant who was previously coded as severe ROP (now coded as no ROP). I thought I copied you on all of those emails but maybe not.

I added "(997 survivors + 223 infants who died)" to the figure legend for figure 2. I think that should make it easy enough to reconcile this figure with what's on figure 1.

I agree with you that it's confusing, but Journal of Perinatology specifically says that the table footnotes should be referenced with Arabic numerals. I've implemented the other minor suggestions.

I'm still waiting for comment from Abhik. Then I think we'll be ready to resubmit this.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030

713 500-6708

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Sunday, July 07, 2013 9:05 PM
To: Kennedy, Kathleen A; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Secondary Final Revision

I have a page of comments and attach.
Thank you very much,
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, July 03, 2013 5:38 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD); Phelps, Dale
Subject: ROP Secondary Final Revision

This is the revision after Lisa's changes. I'm going to send it out again to most of the members of the SUPPORT subcommittee because I received very few replies when I sent it before.

Lisa, thanks for working on this. I have one question about the edits you did. There were a lot of formatting changes to the endnote numbers in the body of the manuscript. I couldn't see what you changed and I had to use my version because I had already made some other changes from comments submitted by others. Let me know if it's something important that I need to do on my version.

I also have a question about the number of "severe ROP" outcomes. I was trying to compare this manuscript to the main SUPPORT manuscript so that I could email Wally about the discrepancy created by the error we uncovered. But there is an even bigger discrepancy between the two manuscripts. The primary manuscript has 41+91=132 infants with non-adjudicated severe ROP and this manuscript has 137. Can you explain that?

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, July 02, 2013 2:21 PM
To: Kennedy, Kathleen A
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Hi Kathleen,
I've attached the updated paper and the two figures that needed to be updated. I noticed a 2 or 3 extra things that I've changed and commented on.
Let me know if you have questions.
I'll be here tomorrow and then out of the office July 4th and 5th.

Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, June 19, 2013 12:31 PM
To: Wrage, Lisa Ann; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thanks for looking into this. I'm glad we got to the bottom of it. I've attached a revision of the manuscript with the changes (in red) that I think we need to make to correct the data error. Nothing important will change but we need to get all the numbers right. There also will be some changes to the figures. I've attached suggested changes (entered as comments on the pdf) for Figure 1. Figure 2 will also have minor changes. I don't think Figures 3 and 4 will look any different, but please verify.

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 19, 2013 9:10 AM
To: Kennedy, Kathleen A; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: FW: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Good Morning,
The Center has replied that the NG03 for this infant is correct: No ROP.
Do you need other information?
Thanks.
Lisa

From: Wrage, Lisa Ann
Sent: Thursday, June 13, 2013 2:47 PM
To: 'Phelps, Dale'; Higgins, Rosemary (NIH/NICHD) [E]; 'Kathleen.A.Kennedy@uth.tmc.edu'
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Our query on this is in process, I'll let you know what we find out.
Thanks.
Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, June 13, 2013 10:10 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Kathleen.A.Kennedy@uth.tmc.edu'; Wrage, Lisa Ann
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Let's see what we learn, and then address this.
I understand the point you are making.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Thursday, June 13, 2013 6:41 AM
To: Phelps, Dale; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'wrage@rti.org'
Cc: 'adas@rti.org'; 'mgantz@rti.org'
Subject: Re: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

The data need to be consistent with the original support report. Probably not worth much more effort for one case.
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 12, 2013 06:14 PM
To: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Wrage, Lisa Ann <wrage@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik <adas@rti.org>; Gantz, Marie <mgantz@rti.org>
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thanks for brining to my attention Kathleen,
My last phrase was final, but should have had a period instead of 'and', thus ending;
Also, of course, the infant's GDB and SUPPORT paper research files.
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, June 12, 2013 2:54 PM
To: Phelps, Dale; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Dale, it looks like you might have intended to say something else when the last sentence ended.

I agree that this outcome (severe ROP in a 27 wk 1200g infant with no subsequent exams available) is highly improbable. I didn't think we needed the story for this manuscript but now I'm worried that it's an error because it's improbable and inconsistent with what's reported in the GDB for this baby. So I think we need to go to the source documents and try to get to the bottom of it before we publish that there was severe ROP on an initial exam at 33 weeks.

Lisa, the next steps would be figuring out what center and what Network number this is. Then we can go back to the coordinator to try to figure it out. If you need some help with this, please let me know.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 12, 2013 2:20 PM
To: Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thank you very much Lisa,

1. The two figures came out very well without color. Nice work.

2. The clinical narrative for the infant "with severe ROP at first examination at 33 weeks PMA" provides very interesting data. It is a very low probability that this 27 week black female who was not SGA and had minimal complications in the hospital course ever had ROP at all. The GDB data says she did have an examination and that there was no ROP.

   Therefore I strongly suspect that the coding on the ROP data-form for SUPPORT was an error.

   This must be queried.

   Can we get paper copies of the ROP exam from the medical record? (HIPAA identifiers blocked out, but Network ID added). Time to go to the source data.

   Also, of course, the infant's GDB and SUPPORT paper research files and

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 12, 2013 11:06 AM
To: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Hi, I've attached the updated paper with responses in comments. Dale, I put a short clinical narrative for the baby with severe ROP at first ROP exam in a comment as well. I've also attached updated figures (the colored figures re-done in black/grey/white), Kathleen let me know what you think. I was skeptical about Figure 4 looking ok without color, but to me it appears doable. I should be able to pretty easily change these shades or line styles, if you prefer.
Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Monday, June 10, 2013 6:45 PM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu
Cc: Archer, Stephanie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

I resent this because I previously sent a version of the document that still had old comments. You can ignore those and use this version.

I've made the suggested changes and reformatted this for Journal of Perinatology. The most recent set of changes are in orange text. There are a couple more questions for **Lisa**. If Lisa can easily find the clinical information about the one infant who had severe ROP on the first exam, that would be great (interesting) but I'm not sure we need it for the resubmission. I had to shorten the abstract. They give a page limit (20 including tables and references) for the manuscript instead of a word limit. We're way over, partly because we have 5 pages of acknowledgments and also because each table was supposed to be on a separate page. I hate to take anything out until we figure out what they really want.

Stephanie, the author instructions say that we need to justify having more than 6 authors. I assume that this goes in the cover letter. Do you have any language that we've used successfully for this in the past?

This journal charges ~$1200 for a color figure. That seems ridiculous to me. I thought the $150 per figure in Pediatrics was bad enough. **Lisa**, can you try again to see if we can get the figures into black and white? I think Figure 2 could be done with shades of gray instead of blue. I'm hoping that figure 4 can be done with different kinds of dashed and dotted lines.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy, MD MPH[1]; Lisa A. Wrage, MPH[2]; Rosemary D. Higgins, MD[3] Neil N. Finer, MD[4]; Waldemar A. Carlo, MD[5]; Michele C. Walsh, MD MS[6]; Abbot R. Laptook, MD[7]; Roger G. Faix, MD[8]; Bradley A. Yoder, MD[8]; Kurt Schibler, MD[9]; Marie G. Gantz, PhD[2]; Abhik Das, PhD[10]; Nancy S. Newman, RN[6]; Wade Rich, RRT[4]; Dale L. Phelps, MD[11]; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
[2] RTI International, Research Triangle Park, NC
[3] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD
[4] University of California at San Diego, San Diego, CA
[5] Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL
[6] Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH
[7] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI
[8] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[9] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH
[10] RTI International, Rockville, MD
[11] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

Address correspondence to:
Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708
FAX: 713 500-0519
Kathleen.A.Kennedy@uth.tmc.edu

Running title: Retinopathy of Prematurity Screening Criteria

Funding source: The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT trial.

Abstract

Objective: To evaluate current retinopathy of prematurity screening guidelines.

Study Design: Data from the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used. Inborn infants 24 $^{0}/_{7}$ to 27 $^{6}/_{7}$ weeks gestational age were enrolled in 2005-2009. Severe retinopathy of prematurity (Type 1 retinopathy of prematurity or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the randomized trial. Examinations followed then current American Academy of Pediatrics screening recommendations.

Results: 997 of the 1121 who survived to first eye exam had final retinopathy of prematurity outcome determined. 137 met criteria for severe retinopathy of prematurity and 128 (93%) of those had sufficient data to determine age of onset of severe retinopathy of prematurity. Postmenstrual age at onset was 32.1 to 53.1 wks. In this referral center cohort, 1.4% developed severe retinopathy of prematurity after discharge.

Conclusion: Our contemporary data support the 2013 screening guidelines. Some infants do not meet treatment criteria until after discharge home.

Keywords (not in title): extremely premature infant

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines[1,2] are based on natural history data from the CRYO-ROP[3] and LIGHT-ROP[4] studies. The CRYO-ROP study[5] remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.[6] Over the past two decades, survival of lower birth weight infants in the US and other developed countries has increased.[7,8] For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.[7] The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age.[3] It rarely occurs before 30 weeks postmenstrual age (PMA, sum of GA at birth and chronological age) or before 4 weeks chronological age. Current American Academy of Pediatrics (AAP) recommendations are for screening to begin by 31 weeks PMA for infants born at 22-27 weeks.[1] The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.[4] Based on the results of the ET-ROP trial, treatment is now recommended for Type 1 ROP, defined as stage 3 in zone I or plus disease with any ROP in zone I, or stage 2 or 3 with plus disease in zone II. Since Type 1 ROP occurs earlier in the course than CRYO-ROP threshold ROP, it is important to determine if screening criteria developed for CRYO-ROP threshold ROP are still appropriate for reliable timely

identification of Type 1 ROP.[9] There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial[10] and a population-based cohort study of infants born 2004-2007 in Sweden[11] reported the age of onset of stages 1, 2, and 3 ROP; however, the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from Canada reported the age of onset of Type 1 ROP in a cohort of 214 infants $\leq$ 27 weeks gestation;[12] this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort[13] reported that "No preterm infants required treatment before the 33rd postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for severe ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 $^{6}/_{7}$ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)[14] to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O_2 saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants.[14] Inborn infants $24\ ^{0}/_{7}$ – $27\ ^{6}/_{7}$ weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 31-33 weeks postmenstrual age, as recommended in the AAP guidelines in place when the study began.[15,16] Subsequent inpatient and outpatient exams were conducted according to the ophthalmologists' established screening procedures at each center. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Study eye exam data were recorded for each exam until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up (including exams after hospital discharge) was curtailed at 55 wks PMA.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants

with Type 1 ROP whose first exam with Type 1 ROP was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. No infants had Type 1 ROP on the initial exam. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for quantiles.[17] Cumulative incidence curves for age of onset of severe ROP and age of maturity were compared by gestational age subgroups (26-27 weeks vs 24-25 weeks) using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-four percent (643/997) of these infants developed ROP and 14% (137/997) developed severe ROP. Among infants with severe ROP, 93% (128/137) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-

Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for ROP are shown in Table 2.[18,19,20] Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p<0.05$ for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3. For the 9 infants with severe ROP and uncertain age of onset, the age of identification ranged from 33.7-40.0 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (lower oxygen saturation and higher oxygen saturation target ranges) and the distributions were similar so only the combined data are shown. The distributions for age of onset of severe ROP for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to prior studies,[3] our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. PMA of onset of severe ROP is significantly later for GA groups 26-27 weeks vs. 24-25 weeks ($p<0.01$). There is no significant difference in the distribution of chronologic age of onset between these two GA groups.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had

mild or moderate ROP (ROP that did not meet criteria for severe ROP). The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop severe ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,[9] so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies[3] in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,[3] lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation by the AAP that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,[1] albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.[21] Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age[22] and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to

chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,[11] which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al[12] included 23-27 week infants; infants ≤25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (24-25 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest ages of onset of Type 1 ROP are more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,[12] the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al[13] that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged

or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study has several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.[23] The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Current AAP screening guidelines, published in 2013,[1] recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines. In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.[23]

Acknowledgments

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Conflict of Interest: The authors declare that they have no financial interests related to the work described in this manuscript.

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Figure Legends:

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all SUPPORT trial infants with known outcome (997 survivors + 223 infants who died)

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP[1] Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/ Moderate ROP	Severe (Type 1 or Treated) ROP
n	1316	997	354	506	137
Gestational age, wks [mean (SD[2])]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.4 (0.9)
Birth weight, g [mean (SD)]	830 (193)	849 (190)	943 (173)	823 (180)	704 (142)
Small for gestational age[3] [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	154 (44)	179 (35)	41 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (45)
Hispanic	259 (20)	190 (19)	69 (19)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (57)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	341 (96)	480 (95)	134 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

[1] Retinopathy of prematurity
[2] Standard deviation
[3] Based on Olsen[24] growth curves

Table 2. Risk factors for ROP[1]

Risk Factor	No ROP[2]	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	354	506	137
Days on supplemental oxygen[3] [median (IQR[4])]	33 (10, 60)	59 (31, 94)	95 (68, 119)
Late-onset sepsis (+ culture) [(n (%)]	75 (21)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	15[5] (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	69[5] (14)	29 (21)
Proven necrotizing enterocolitis[6] [n (%)]	20 (6)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	123 (35)	271 (54)	94 (69)

[1] Retinopathy of prematurity
[2] $p<0.05$ for all comparisons of No ROP vs Any ROP (mild, moderate, or severe)
[3] Tabulated until 120 days or discharge if discharged sooner, among infants who survived to discharge, transfer or 120 days
[4] Interquartile range
[5] Missing data for 1 infant
[6] Modified Bell's stage II or III[25]

Table 3. Postmenstrual and chronological age of onset[1] [with 95% confidence intervals (CI[2])] of any stage ROP[3] (among infants with ROP age of onset determined)

		Postmenstrual Age (weeks)								
ROP type	n	Min[4]	1%	5%	25%	50%	75%	95%	99%	Max[4]
Any ROP (95%CI)	634	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP[5] (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

		Chronological Age (weeks)								
ROP type	n	Min	1%	5%	25%	50%	75%	95%	99%	Max
Any ROP (95%CI)	634	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP[3] (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

(95% CI)										

[1] Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.
[2] Confidence interval
[3] Retinopathy of prematurity
[4] Min = minimum age at which designated severity of ROP was identified; max = maximum age.
[5] Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP[1] criteria in relation to discharge and transfer

Infants with Severe ROP N=137	First exam with severe ROP occurred before discharge to home n=123	First exam with severe ROP criteria occurred after discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks [median, range]	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks [median, range]	42.5 (37.7-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital [n]	1	4

[1] Retinopathy of prematurity

Table 5. ROP[1] exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I [n (%)]	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone [n (%)]	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP [n (%)]	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone [n (%)]	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP [n (%)]	0	121 (23%)
Plus disease [n (%)]	0	0
No exam prior to discharge [n (%)]	0	3
Unknown (missing or incomplete information on exam prior to discharge) [n (%)]	0	5

[1] Retinopathy of prematurity

Table 6. Risk factors for ROP[1] for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, g [mean (SD)]	701 (103)	872 (185)
GA[2] at birth, wks [mean (SD)]	25.7 (0.9)	26.4 (1.0)
Days on oxygen [mean (SD)]	59 (27)	47 (33)
Early onset sepsis [n (%)]	0	10 (2)
Late onset sepsis [n (%)]	7 (50)	148 (28)
Fungal sepsis [n (%)]	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	0	59 (11.1)
Proven necrotizing enterocolitis [n (%)]	1 (7)	36 (7)
Patent ductus arteriosus [n (%)]	11 (79)	258 (48)
Discharge on oxygen [n (%)]	2 (14)	88 (16)

[1] Retinopathy of prematurity
[2] Gestational age

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Friday, July 12, 2013 11:05:42 AM

Wally

Have you had a chance to look at it yet?

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 11, 2013 12:38 PM
To: Das, Abhik; Wally Carlo, M.D.; Finer, Neil
Cc: wcarlo2@gmail.com
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

I would be ok with this going to the SC and SUPPORT investigators

Thanks
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, July 09, 2013 10:51 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo2@gmail.com
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Importance: High

Wally and Neil:

The steering committee wants us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have formulated the attached draft response that has been vetted by the legal folks at RTI. Please take a look and send me any changes. Once we

agree on the draft, I will send on to the steering committee for their concurrence.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
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email: mcarome@citizen.org
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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Resubmission of ROP Secondary Paper
Date: Thursday, July 11, 2013 11:03:21 AM
Attachments: ROP Natural History Study Manuscript (final revision for J Perinatol, no figures).doc
Figure 2 (revised).pdf
Figure 1 (revised).pdf
Figure 4 (B&W).pdf
Figure 3.pdf

This is the second email I sent. Still no response from Abhik or Nancy. It took an email from you last time to get Nancy to respond.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Kennedy, Kathleen A
Sent: Wednesday, July 03, 2013 7:48 AM
To: 'Das, Abhik'; 'nfiner@ucsd.edu'; 'Gantz, Marie'; 'nxs5@cwru.edu'; 'wrich@ucsd.edu'; 'kurt.schibler@cchmc.org'; 'Michele.Walsh@UHhospitals.org'; 'Bradley.Yoder@hsc.utah.edu'
Cc: Archer, Stephanie
Subject: Resubmission of ROP Secondary Paper

I have not received an acceptance or comments from you on the revision that I sent on 6/13, so I'm resending the final revision again. If you wish to remain an author on this, please send your comments or approval by **July 10**. Thanks.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Stevens, Timothy"
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publications | Stevens, Respiratory Outcomes of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)
Date: Thursday, July 11, 2013 9:27:11 AM

Tim –
Both of them were the FU PI's during the course of the study – Stephnaie can draft an authorship contribution section for you.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Wednesday, July 10, 2013 10:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Publications | Stevens, Respiratory Outcomes of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Hi Rose

As you know, Pediatrics pushed back against the length of our author list. Is the author list set? I am not sure Michael Accarregui or Gary Myers contributed significantly to Breathing Outcomes because they were out of the network for the bulk of the study. I have had no communication from either related to Breathing Outcomes.

Should I include them or is it ok to leave them off the list?

Thanks

Tim

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, June 25, 2013 10:05 AM
To: Neil Finer (nfiner@ucsd.edu); Wally Carlo (wacarlo@uab.edu); Higgins, Rosemary (NIH/NICHD) [E];

Mike O`Shea (moshea@wfubmc.edu); Charles Bauer (cbauer@peds.med.miami.edu); Ricki Goldstein (golds005@mc.duke.edu); Janell Fuller (JaFuller@salud.unm.edu); Mike Acarregui (Michael.Acarregui@providence.org); Susan Hintz (srhintz@stanford.edu); Athina Pappas (apappas@med.wayne.edu); Anna Bodnar (annabodnar.ab@gmail.com); Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org); Ira Adams-Chapman (iadamsc@emory.edu); Yvonne Vaucher (yvaucher@ucsd.edu); Patricia Evans (Patricia.W.Evans@uth.tmc.edu); Roy Heyne (Roy.Heyne@utsouthwestern.edu); Kim Yolton (kimberly.yolton@cchmc.org); Dee Wilson (b)(5) @aol.com); Betty Vohr (bvohr@wihri.org); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Nancy Newman (nxs5@cwru.edu); Wade Rich (wrich@ucsd.edu); Kurt Schibler (kurt.schibler@cchmc.org); Barbara Do (bdo@rti.org); Abhik Das (adas@rti.org); Jamie Newman (newman@rti.org); Roger Faix (roger.faix@hsc.utah.edu); Brad Yoder (bradley.yoder@hsc.utah.edu); Abbot Laptook (alaptook@wihri.org); Marie Gantz (mgantz@rti.org); Michele Walsh (Michele.walsh@cwru.edu); Phelps, Dale; Szilagyi, Peter
Cc: Stevens, Timothy
Subject: Publications | Stevens, Respiratory Outcomes of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Attached is a revised version of Tim's paper for your review. Please send all comments to him.

Thank you,

Stephanie

Stephanie Wilson Archer
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Monday, June 24, 2013 10:06 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: revised manuscript

Hi Rose and Stephanie,

Attached is the revised manuscript including tables and figures as well as my reply to the editor and reviewers. Can you please forward to the coauthors?

A couple things:

- In the document entitled reply to reviewers, I copied the text from the Pediatrics Decision letter, bolded the editor and reviewer comments and wrote my reply in red font. I hope this will make reviewing my replies easier.
- Below I copied the two comments made by the editor (bold) along with my replies (italics).
  1. **"It appears that not all the coauthors listed meet the authorship criteria."**
     Stephanie – can you update the author list and their roles? If there is an appropriate

way to shorten the author list, it may help us. We will need to make this as strong as possible.

2. **"Please address the ethical concerns about the original study."**

   In a letter dated June 4th, 2013, Lisa Buchanan, Compliance Officer for the Department of Health and Human Service's Office of Human Research Protection (OHRP), stated that "OHRP does not and never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent." In addition, she writes, "we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic. In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further action in studies involving similar designs until the process of producing appropriate guidance is completed." (http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf).

   Based upon these comments, the following sentences have been added to the revised manuscript, "The SUPPORT Study and its design were deemed ethical by the Department of Health and Human Service's Office of Human Research Protection (OHRP). OHRP has initiated a public discussion of the adequacy of the written informed consent used in SUPPORT and similar trials of clinical practices that are within the range of standard of care at the time the research study was performed."

I'd like to have all replies by July 4th if possible.

Thanks for your help

Tim

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: FW: BMJ Press Release Embargo 23:30 hours (UK time) Tuesday 9 July 2013
Date: Wednesday, July 10, 2013 1:55:10 PM
Attachments: bmj.f4198.pdf

FYI,

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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1700 6th Avenue South
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From: Brocklehurst, Peter [mailto:p.brocklehurst@ucl.ac.uk]
Sent: Wednesday, July 10, 2013 3:16 AM
To: William Tarnow-Mordi; Brian Darlow; Schmidt, Barbara (Neonatology) (barbara.schmidt@uphs.upenn.edu); Wally Carlo, M.D.
Cc: 'Stenson, Ben'
Subject: RE: BMJ Press Release Embargo 23:30 hours (UK time) Tuesday 9 July 2013

Apologies – I meant to attach the article pdf.

From: Brocklehurst, Peter
Sent: 10 July 2013 09:00
To: William Tarnow-Mordi; Brian Darlow; Schmidt, Barbara (Neonatology) (barbara.schmidt@uphs.upenn.edu); 'Wally Carlo, M.D.'
Cc: Stenson, Ben
Subject: FW: BMJ Press Release Embargo 23:30 hours (UK time) Tuesday 9 July 2013

Dear all

Please see correspondence below received by Ben last night. This is rather unfortunate as it has the potential to cause more disruption to neonatal research and to each of our trials. Given that we have to give some response to the journalist, Ben and I feel that we have to press on with drafting a response today from the UK trial. We will of course share this with you, but we don't have the time to produce a co-ordinated response from all the trials. If we fail to respond soon, then there may be no response from us and that would be much worse, given the nature and tone of the press release by the BMJ.

Similarly I think it would be helpful for each of you to consider submitting a rapid response to the BMJ from your own perspectives – again, this needs to be timely, so cannot be a joint response.

We will keep you informed of progress as it develops during the day.

With best wishes

Peter

From: Ella Pickover [mailto:ella.pickover@pressassociation.com]
Sent: 09 July 2013 12:47
To: Stenson, Ben
Subject: FW: BMJ Press Release Embargo 23:30 hours (UK time) Tuesday 9 July 2013

Hello Dr Stenson,
I've been trying to reach someone about the Boost study mentioned in the below article. I'm writing a news story based on the article, would you like to respond? Particularly I'd be keen to find out whether you believe that your study obtained adequate consent?
Best wishes,
Ella

Ella Pickover
Health Correspondent
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292 Vauxhall Bridge Road, London, SW1V 1AE

From: edickinson@bmjgroup.com [mailto:edickinson@bmjgroup.com]
Sent: 05 July 2013 16:49
To: Ella Pickover
Subject: BMJ Press Release Embargo 23:30 hours (UK time) Tuesday 9 July 2013

BMJ Press Release
Embargo 23:30 hours (UK time) Tuesday 9 July 2013

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Senior doctor calls on governments to investigate possible lack of informed consent in premature baby studies

Concerns over ethics of trial may have global implications

Observations: US study criticized for experimentation with premature infants

In an article on bmj.com, a senior doctor today calls on several governments around the world to investigate whether parents of premature babies were fully informed of the risks of a study on the health effects of varying oxygen levels, as was not the case in the US.

Dr Sidney Wolfe, founder and senior adviser to the Health Research Group at Public Citizen, says it is surprising that the adequacy of consent forms for nearly identical studies in the UK, Australia, New Zealand, Canada, and other countries with similar regulation of human research, has apparently not yet been examined.

He argues that there may well be "serious problems" with such risk disclosure that must be addressed.

The study, called SUPPORT, was funded by the US National Institutes of Health and took place at many universities across the US between 2005 and 2009. A total of 1,316 extremely premature infants were randomly maintained at either higher (91-95%) or lower (85-89%) ranges of oxygen saturation.

The main aim of the study was to see whether the infants were more likely to die or suffer eye damage and blindness at the different oxygen ranges.

Wolfe says that parents were not adequately informed about the risks or true nature and purpose of the research, but others have staunchly defended this lack of informed consent.

He argues that information on risks and possible outcomes was missing from the consent forms, and that the forms "failed to distinguish the important differences between these clearly experimental procedures for managing the oxygen therapy and the usual individualized standard of care the babies would have received had they not been enrolled in the study."

Worse, he adds, "many of the consent forms falsely stated that because all of the treatments proposed in

this study are 'standard of care' there would be no expected increase in risk to the infants."

Others, however, defend the lack of appropriate informed consent. In a recent BMJ editorial, eminent neonatologist Neena Modi implicitly argued that withholding some risk information would "reduce the burden of decision making at difficult and stressful times" and "would also reduce the risk of 'injurious misconception,' where participation is inappropriately rejected because of an exaggerated and disproportionate perception of risk."

But Wolfe suggests that the underlying principle behind these arguments "is that it is necessary, via inadequately informed consent, to blur the line between research and standard of care to facilitate more consent and participation."

This, he concludes, "appears to be exactly what occurred when consent was obtained for the SUPPORT study subjects."

Contact:
Sidney M Wolfe, Founder and senior adviser, Health Research Group, Public Citizen, Washington, DC, USA
Tel: +1 202 588 7735
Email: Swolfe@citizen.org

Embargoed link to full article: http://press.psprings.co.uk/bmj/july/wolfeobs.pdf
Public link once embargo lifts: http://www.bmj.com/cgi/doi/10.1136/bmj.f4198
Link to Neena Modi editorial (published 12 June 2013): http://press.psprings.co.uk/bmj/july/modi.pdf

Embargo 23:30 hours (UK time) Tuesday 9 July 2013

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BMJ

BMJ 2013;347:f4198 doi: 10.1136/bmj.f4198 (Published 9 July 2013)

OBSERVATIONS

THE WASHINGTON BRIEF

US study criticized for experimentation with premature infants

Sidney M Wolfe *founder and senior adviser at the Health Research Group at Public Citizen*

Washington, DC

Recently there have been strong, public arguments in the United States criticizing the lack of informed consent concerning risks in a US National Institutes of Health (NIH)-funded multi-center study called SUPPORT, which randomized 1316 extremely premature babies—average weight 2 lb, average gestation 26 weeks—to be maintained at higher (91-95%) or lower (85-89%) oxygen saturation levels after delivery. Conversely, investigators involved in this study, some ethicists, the NIH Director and his top officials and others, including medical journals, have staunchly defended this lack of informed consent. What underlies this sharp disagreement? Central to this dispute are conflicting views as to whether SUPPORT and similar studies are more like experiments or more like the existing standards of care.

In March, the US government's Office of Human Research Protections (OHRP), pursuant to a complaint about the SUPPORT study two years ago, concluded its investigation with a letter[1] to the lead site in the trial, the University of Alabama in Birmingham (UAB), criticizing multiple instances of the lack of information about risks in the consent forms,[2] compared with the discussion of such risks in the protocol for the study.[3]

In particular, the study protocol makes clear that the purpose of this study was to determine whether the combination of death or eye damage were more common in the higher or lower oxygen target group, but information about the fact that both of these serious outcomes could differ depending on which group the baby was randomized to was missing from the consent form.

In addition to the OHRP criticisms, there are additional serious problems.[4] Although the protocol from the study stated that the high oxygen saturation target (91% to 95%) was considered "more conventional" by the investigators, none of the consent forms disclosed this implicit admission that lower oxygen was less conventional. The protocol also described the experimental procedure of using pulse oximeters intentionally miscalibrated to provide the medical teams caring for the premature babies in the study with oxygen saturation readings, either inaccurately low, for the high oxygen babies or inaccurately high, for the low oxygen babies, to keep the doctors and nurses unaware to which oxygen group any baby in the experiment had been randomized. This miscalibration was only disclosed in half of the 22 consent forms, but none explained how this experimental procedure could have affected important clinical decisions related to the babies' care, such as whether to intubate or extubate the babies.

More broadly, the consent forms, although required to do so by regulations governing human experimentation, failed to distinguish the important differences between these clearly experimental procedures for managing the oxygen therapy and the usual individualized standard of care the babies would have received had they not been enrolled in the study. Worse, many of the consent forms falsely stated that because all of the treatments proposed in this study are "standard of care," there would be no expected increase in risk to the infants.

In attacking the criticisms from the OHRP, an editorial in the *New England Journal of Medicine* stated that the consent form, approved by all of the institutional review boards, "addressed the prevalent knowledge fairly and reasonably."[5] SUPPORT investigators, defending the lack of inclusion of the risk of death in the consent form, wrote that "Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected."[6] Thus, they are saying that because they did not expect an increased rate of death in the low oxygen group, this clearly possible risk did not need to be disclosed in the consent forms. The fact that death was one of the primary stated outcomes of the study seems to have escaped them.

A recent editorial in this journal by eminent neonatologist Neena Modi stated that "Illogical regulation, as reflected in this [OHRP] response, and poor integration of research with day to day clinical practice delay the incremental advances that are essential to improve care . . . a paradigm shift is needed, **involving acceptance of randomised allocation of treatments already widely used as a standard of care** (emphasis supplied) . . . randomisation would be the recommended default and that

Swolfe@citizen.org

patients would be offered the opportunity to opt out, rather than invited to opt in. This would reduce the burden of decision making at difficult and stressful times. It would also reduce the risk of 'injurious misconception,' where participation is inappropriately rejected because of an exaggerated and disproportionate perception of risk."[7]

Modi had earlier elaborated on this by stating "To seek truly informed consent for participation in a research study is to oblige parents to listen to complex medical arguments that spell out the uncertainties of current practice. Although it might be argued that parents have a right to know about all aspects of their baby's care, this would mean that, in many instances, distressed parents were forced to make decisions that they would not normally be asked to make."[8]

The underlying principle behind these arguments opposing fully informed consent in experiments is that it is necessary, via inadequately informed consent, to blur the line between research and standard of care to facilitate more consent and participation, which appears to be exactly what occurred when consent was obtained for the SUPPORT study subjects. Given that there were almost identical studies, coordinated with the SUPPORT group, in the UK, Australia, New Zealand, Canada, and other countries that have similar, if not identical regulation of human research, it is surprising that, to our knowledge, government authorities in those countries have not investigated the adequacy of those consent forms.

Competing interests: SMW, along with Michael Carome, now director of the Health Research Group, have previously written to HHS protesting the lack of informed consent in the SUPPORT study: http://www.citizen.org/hrg2111 and http://www.citizen.org/documents/2124.pdf.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Office for Human Research Protections. Letter to the University of Alabama at Birmingham, 7 March, 2013. www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf.
2 Consent form for the SUPPORT trial. www.citizen.org/documents/support-study-consent-form.pdf.
3 NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised 16 September 2004; updated 28 March 2005). www.nih.gov/icd/od/foia/library/Protocol.pdf.
4 Public Citizen. Letter to Kathleen Sebelius, secretary, Department of Health and Human Services, Washington, DC. www.citizen.org/documents/2124.pdf.
5 Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med* published online 17 April 2013.
6 Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med* published online on 17 April 2013.
7 Modi N. How not to reduce uncertainties in care. *BMJ* 2013;346:f3786.
8 Modi N. Informed consent difficult in paediatric intensive care. *BMJ* 1993;307:1495.

Cite this as: *BMJ* 2013;347:f4198

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, July 10, 2013 1:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Jarman, John (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Attachments: ATT00001.htm; ATT00002.htm

FYI...nothing needs doing at this point, but wanted you to know.

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, July 10, 2013 12:24 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Fwd: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

> **From:** "Barros, Colleen (NIH/OD) [E]" <BarrosC@od.nih.gov>
> **Date:** July 9, 2013, 1:01:01 PM EDT
> **To:** "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>, "Tabak, Lawrence (NIH/OD) [E]" <Lawrence.Tabak@nih.gov>
> **Cc:** "Servis, Suzanne (NIH/OD) [E]" <ServisS@OD.NIH.GOV>, "Barros, Colleen (NIH/OD) [E]" <BarrosC@od.nih.gov>
> **Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)**
>
> Kathy-----perhaps this one got by you. Can you let us know? The IG contacted us again about a contact point as they want to start. Larry thought it should be you but please let us know if you think it should be someone else. Thanks.

From: Barros, Colleen (NIH/OD) [E]
Sent: Friday, June 28, 2013 1:16 PM
To: Tabak, Lawrence (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Barros, Colleen (NIH/OD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Importance: High

Kathy--+-I spoke to Larry re this. He thought it might be you as contact point. Agree? Short fuse.

From: Servis, Suzanne (NIH/OD) [E]
Sent: Thursday, June 27, 2013 4:29 PM
To: Barros, Colleen (NIH/OD) [E]
Cc: Stein, Meredith (NIH/OD) [E]; Allen, Gail (NIH/OD) [E]
Subject: FW: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)
Importance: High

ISSUE: Who at NIH should talk to the OIG about the SUPPORT Study?

Colleen, attached and included below is info about a new review by the OIG Office of Evaluations and Inspections related to the SUPPORT Study (see attached NYT article to refresh your memory). The OIG inspectors are asking to talk to the following NIH officials the week of July 7 (!):

- Francis S. Collins, M.D., Ph.D.,
- Alan E. Guttmacher, M.D.,
- Kathy L. Hudson, Ph.D., and
- Rosemary Higgins, M.D.

They will ask them the following questions:

- When did NIH become aware of OHRP's review of the SUPPORT trial and UAB?
- What was NIH's involvement in OHRP's review?
- Did NIH express any concerns about the informed consent document?
- From NIH's perspective, was the conduct of OHRP's review typical?
    - Why or why not?
- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

I am asking your advice about who at NIH should talk to the OIG Inspectors. We can discuss at your convenience, although it sounds like the OIG would like to move quickly. Thank you, Suzanne

Suzanne J. Servis
Director, Office of Management Assessment
Office of the Director
National Institutes of Health
6011 Executive Boulevard, Suite 601
Rockville, MD 20852
Phone: 301-496-1873
Fax: 301-480-1204

From: Brown, Tiffany (NIH/OD) [E]
Sent: Thursday, June 27, 2013 4:14 PM

To: Servis, Suzanne (NIH/OD) [E]
Cc: Monickam, Sarah (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]
Subject: Upcoming OIG Review: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Hi Suzanne,

Per our discussion, I am attaching the information on the OIG's upcoming review entitled, "*Office of Human Research Protections Oversight of the SUPPORT Clinical Trial*" (OEI-01-13-00420). Please let Meredith and myself know the outcome of your discussion with Colleen.

I know that you said that you didn't really need the memo, but I included the link, for your convenience: http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf.

This is the request from the OIG (start notice is attached):

OIG is currently conducting a study, *Office for Human Research Protections Oversight of the SUPPORT Clinical Trial*, (OEI-01-13-00420). This Congressionally requested study will examine the extent to which the Office for Human Research Protections (OHRP) followed procedures and exercised its discretion in its compliance evaluation of the SUPPORT clinical trial (start notice attached). As a part of this review, we would like to meet with NIH to discuss its role in OHRP's oversight of the SUPPORT trial and the University of Alabama Birmingham (UAB). We are available to meet the week of July 7th (except, Tuesday, July 9th).

We would like to meet with the following NIH officials:

- Francis S. Collins, M.D., Ph.D.,
- Alan E. Guttmacher, M.D.,
- Kathy L. Hudson, Ph.D., and
- Rosemary Higgins, M.D.

Our general questions include the following:

- When did NIH become aware of OHRP's review of the SUPPORT trial and UAB?
- What was NIH's involvement in OHRP's review?
- Did NIH express any concerns about the informed consent document?
- From NIH's perspective, was the conduct of OHRP's review typical?
    - Why or why not?
- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

Thanks!

TIFFANY BROWN
NIH/OD/OMA

(301) 496-2464 - DIRECT
(301) 402-0169 - FAX

From: Finer, Neil
To: Das, Abhik; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo2@gmail.com
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Tuesday, July 09, 2013 9:15:03 PM

Hi Rose
This sounds like a proper and appropriate response
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, July 09, 2013 7:51 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo2@gmail.com
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Importance: High

Wally and Neil:

The steering committee wants us to formulate a response to the letter requesting SUPPORT data (attached as reference), to be sent on its behalf. I have formulated the attached draft response that has been vetted by the legal folks at RTI. Please take a look and send me any changes. Once we agree on the draft, I will send on to the steering committee for their concurrence.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org

web: www.citizen.org

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: Re: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions
Date: Saturday, July 06, 2013 7:07:40 PM

Given our UAB's lawsuit, it may ne best for me not to attend.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Finer, Neil" <nfiner@ucsd.edu>
Cc: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Sat, Jul 6, 2013 21:46:17 GMT+00:00
Subject: Re: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions

Neil
I have registered and plan on attending. My understanding is this is an open meeting and folks can attend so up to you
Thanks
Rose

Sent from my iPhone

On Jul 6, 2013, at 4:42 PM, "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>> wrote:

Hi Rose
I think it may be appropriate for you and me to go to this
Are you planning to attend?
Please let me know if you think that I should be there
Thanks
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, July 04, 2013 12:36 PM
To: Finer, Neil
Subject: Re: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions

Hi Neil.

Because we have a law suit, I assumed I should not go to prevent the risks of saying something that Public Citizens will use against me in the law suit.

I think it may be good for Rose and you to go but you may want to check with USD.

I met withIRB consultants UAB is using. It is interesting how far their beliefs in what should be done differs with our SC members and how their ideas on SUPPORT differ from ours.
Wally

-----Original message-----
From: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>
Sent: Thu, Jul 4, 2013 18:18:34 GMT+00:00
Subject: FW: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions
Wally
Do you plan on going to this?
It may be a good thing if we are both there
Your thoughts?
Happy July 4
Neil

-----Original Message-----
From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Wednesday, June 26, 2013 1:51 PM
To: Wally Carlo; Finer, Neil; Krisa P Van Meurs (vanmeurs@stanford.edu<mailto:vanmeurs@stanford.edu>); Uday Devaskar; Kristi Watterberg; Bill Truog; Kathleen Kennedy; Jon Tyson; Pablo Sanchez; Brenda Poindexter; Seetha Shankaran; Michele Walsh; Leif Nelin; Kurt Schibler; Barbara Stoll; Ron Goldberg; Barbara Schmidt; Abbot Laptook; Carl D'Angio; Abhik Das
Cc: Rosemary Higgins
Subject: FW: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions

FYI

-----Original Message-----
From: Office for Human Research Protections (OHRP) [mailto:OHRP-L@list.nih.gov] On Behalf Of Irene Stith-Coleman
Sent: Wednesday, June 26, 2013 3:21 PM
To: OHRP-L@list.nih.gov<mailto:OHRP-L@list.nih.gov>
Subject: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions

On June 26, 2013, the Department of Health and Human Services (HHS) announced in the Federal Register an August 28, 2013 public meeting to seek public input and comment on how certain provisions of the Federal policy for the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically requests input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process.

HHS is seeking participation in the meeting and written comments from all interested parties, including, but not limited to, IRB members, IRB staff, institutional officials, research institutions, investigators, research subject advocacy groups, ethicists, and the regulated community at large. The meeting and the written comments are intended to assist HHS, through the Office for Human Research Protections (OHRP), Office of the Assistant Secretary for Health (OASH), in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects. HHS is seeking input on a number of specific questions but is interested in any other pertinent information participants in the public meeting would like to share.

The public meeting will be held on August 28, 2013, from 9 a.m. to 5 p.m., in the Hubert H. Humphrey Building, 200 Independence Ave., SW, Great Hall, Washington, DC 20201; Metro: Federal Center SW

station.

Deadline for Registering to Attend the Pubic Meeting:
While there is no registration fee, individuals planning to attend the public meeting in person must register to attend. Registration to attend the meeting will be accepted on a first-come, first-served basis and must be received no later than 5 p.m. on August 14, 2013. Due to space limitations, the number of registrants will be capped.

Deadline for Registering to Present at the Public Meeting:
Registration to present at the public meeting will be accepted on a first-come, first-served basis and must be received no later than 5 p.m. on August 7, 2013.

Deadline for Submitting Comments for the Public Meeting:
Written comments for discussion at the public meeting must be received no later than 5 p.m. on August 7, 2013.
Deadline for Submitting Comments after the Public Meeting

In addition to materials submitted for discussion at the public meeting, individuals may submit other written comments after the public meeting. These comments must be received no later than 5 p.m. on September 9, 2013 for consideration by HHS.

An alternative to attending the meeting in person will be provided. Participants who cannot attend the public meeting in person will have an option to view it via live streaming technology. Information on that option will be posted at a later time on the OHRP website at http://www.hhs.gov/ohrp.

The Federal Register notice announcing the public meeting and details about the following: registering to attend, registering to present at the meeting, submitting written comments, viewi

From: Wally Carlo, M.D.
To: Shankaran, Seetha; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"; carl_dangio@urmc.rochester.edu; Truog, William (MD) (wtruog@cmh.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Krisa Van Meurs (vanmeurs@stanford.edu) (vanmeurs@stanford.edu); cotte010@mc.duke.edu; Walsh, Michele
Subject: Re: SUPPORT Webinar from Bloomberg BNA
Date: Friday, July 05, 2013 3:57:32 PM

Yes. Most of us got the info.

Wally

-----Original message-----

From: "Shankaran, Seetha" <sshankar@med.wayne.edu>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "rosemary.higgins@nih.gov" <rosemary.higgins@nih.gov>, "'nfiner@ucsd.edu'" <nfiner@ucsd.edu>, "carl_dangio@urmc.rochester.edu" <carl_dangio@urmc.rochester.edu>, "Truog, William (MD) (wtruog@cmh.edu)" <wtruog@cmh.edu>, "Kristi Watterberg (kwatterberg@salud.unm.edu)" <kwatterberg@salud.unm.edu>, "Krisa Van Meurs (vanmeurs@stanford.edu) (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "Walsh, Michele" <Michele.Walsh@UHhospitals.org>
Sent: Fri, Jul 5, 2013 19:47:20 GMT+00:00
Subject: FW: SUPPORT Webinar from Bloomberg BNA

Hi all
Were you aware of this Webinar coming up? The IRB here informed us of it.
Seetha

A webinar on the SUPPORT study has been announced by Bloomberg BNA:

http://www.bna.com/support-trial-oxygen-w17179874408/

The SUPPORT Trial on Oxygen Therapy in Premature Infants: Ethical and Regulatory Issues

The SUPPORT Trial on Oxygen Therapy in Premature Infants: Ethical and Regulatory Issues

[$224 Live webinar \/]
Wednesday, July 17, 2013
1:00 PM - 2:30 PM ET
Product Code - LGA167
Speaker(s): Moderator: Michele Russell-Einhorn, J.D., Dana-Farber Cancer Institute; Arthur L. Caplan, Ph.D., New York University Langone Medical Center;

Michael A. Carome, M.D., FACP, Public Citizen

The Surfactant, Positive Pressure and Oxygenation Randomized Trial (SUPPORT), which looked at the health outcomes of premature infants given different levels of supplementary oxygen, gained notoriety after the Department of Health and Human Services Office for Human Research Protections (OHRP) issued a compliance determination letter in March of 2013 raising serious concerns about the lack of information in, and comprehensiveness of, the research consent forms approved by the 23 institutions participating in this research. The OHRP determination letter was followed by several communications from the public advocacy group Public Citizen affirming the OHRP determination of compliance issues but going further and alleging that the egregious nature of the insufficiencies exceeded what was flagged by the government.

These communications generated controversy resulting in many opinion pieces and editorials published in the New England Journal of Medicine as well as the New York Times--some supporting the trial and criticizing the critics, others supporting the government and Public Citizen.

In addition, a lawsuit has been filed against the University of Alabama, the lead site in the study, alleging that the premature babies enrolled in the study were subjected to research that was unethically designed and exposed the subjects to undisclosed and unacceptable risks of death and blindness.

What are the issues raised by this controversy over the SUPPORT study? How does this impact Institutional Review Board (IRB) review of randomized studies? How might it influence future studies of comparative effectiveness? The faculty for this program will address these issues, with representation from those on each side of the debate.

Educational Objectives:

- Understand the regulatory requirements for Institutional Review Board (IRB) review of research.
- Learn about the complexities of research informed consent requirements and randomized clinical trials.
- Discover how usual routine clinical care differs from research interventions in a clinical trial.

Who would benefit most from attending the program?

Researchers; Institutional Review Board (IRB) members and staff; research compliance staff; health care attorneys.

Program Level: Advanced.

Credit Available: CLE. For more information, please click on the "CLE Credit" tab.

From: Namasivayam Ambalavanan
To: Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan
Cc: Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Fourth draft of July 5, 2013
Date: Friday, July 05, 2013 11:36:03 AM
Attachments: PCO2_SUPPORT_July5_2013.docx

Dear All,
Here is the much-awaited fourth draft of our manuscript examining PCO2 in SUPPORT. The main changes in this draft are:

1) Thanks to much work by Lisa Wrage, the main results are now the adjusted results, and the unadjusted results have been moved to Supplemental Tables
2) Some clarifications of methods and explanations in Discussion.
3) A few novel results. Eg. an interaction between PCO2 and SpO2 for severe IVH, again suggesting that sicker kids are more likely to have worse outcomes. Again, this is what we'd expect, but I suppose we should not always hope for unexpected findings.

Thanks,
Ambal

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Tuesday, March 05, 2013 12:54 PM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,
Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
2) Developed a new table of adjusted results
3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis (Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,
Best regards,
Ambal

From: Namasivayam Ambalavanan
Sent: Thursday, February 21, 2013 10:37 AM
To: Kennedy, Kathleen A; Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: PaCO2 manuscript : first draft of Feb21, 2013
Importance: High

Dear All,
Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.
(Stephanie: Would you check the boilerplate and grant acknowledgments?)
Thank you for all your help,
Best regards,
Ambal

Namasivayam Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology
University of Alabama at Birmingham
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176F Suite 9380, Women and Infants Center
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Tel Office (205) 934 4680 *Lab (205) 934 0751 or 996 5419*
Fax Office (205) 934-3100 *Lab (205) 996 2333*
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Wednesday, February 02, 2011 10:06 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,
Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,
Thank you for all your help,
Ambal

From: Namasivayam Ambalavanan
Sent: Mon 11/8/2010 5:40 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu; higginsr@mail.nih.gov
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,
Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.
Thank you,
Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,
Ambal

N. Ambalavanan MD
Professor, Division of Neonatology
Departments of Pediatrics, Cell Biology, and Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333
Email ambal@uab.edu

From: Namasivayam Ambalavanan
Sent: Sun 10/31/2010 6:25 PM
To: Namasivayam Ambalavanan; Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.
Ambal
(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

From: Namasivayam Ambalavanan
Sent: Sat 10/30/2010 8:15 PM
To: Kennedy, Kathleen A; ambal@uab.edu
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.
Regarding Michele's excellent questions:
1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)
>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.
>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.
Thanks,
Ambal

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Sat 10/30/2010 4:59 PM
To: Namasivayam Ambalavanan
Cc: Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann
Subject: RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program

UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Saturday, October 30, 2010 10:18 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.
I have two questions that I think are pertinent:
1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)
Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.
Best Michele

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Fri 10/29/2010 5:28 PM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT: First draft

Dear All,
Attached is the first full draft of the PAS abstract on PaCO2 in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how).
Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?
Thanks,
Ambal

N. Ambalavanan MD
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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 *Lab (205) 996 2333*
Email ambal@uab.edu

From: Namasivayam Ambalavanan

Sent: Saturday, October 23, 2010 7:16 AM
To: Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO2 (using highest FiO2 on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?
Ambal

From: Namasivayam Ambalavanan
Sent: Fri 10/22/2010 8:58 PM
To: Michael Cotten; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran
Subject: RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO2 (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO2 and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO2. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO2 were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.
Ambal

From: Michael Cotten [mailto:cotte010@mc.duke.edu]
Sent: Fri 10/22/2010 7:57 PM
To: Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal
Cc: Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon
Subject: Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co2? Some babies are easily hyperventilatable, and sometimes practtioners allow co2 to be hoigh on min settings,,,,and those kids are probably way different than kids pn high sttings or hfv who remain hypercarbic,,,

Mc

From: "Namasivayam Ambalavanan" [NAmbalavanan@peds.uab.edu]
Sent: 10/22/2010 03:59 PM EST
To: "Wrage, Lisa Ann" <wrage@rti.org>; <ambal@uab.edu>
Cc: "Das, Abhik" <adas@rti.org>; "Gantz, Marie" <mgantz@rti.org>; "Wally Carlo, M.D."

<WCarlo@peds.uab.edu>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; "Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>; <Michele.Walsh@UHhospitals.org>; Michael Cotten; "Laughon, Matthew M" <matt_laughon@med.unc.edu>
Subject: RE: PAS ABSTRACT

Hi Lisa,
(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO2 (especially higher PaCO2 and fluctuating PaCO2) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO2 is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal $PaCO_2$, minimal $PaCO_2$, time-weighted $PaCO_2$, and SD of $PaCO_2$ as independent continuous variables with actual time-weighted PaO_2 (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPROM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO2 for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).
The results of the logistic regression should give us an idea of the association of the PaCO2 variables with outcome, after adjustment for the other variables. We probably do not need PaCO2 values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO2 and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO2 terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO2 to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO2 category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO2 categories and the numbers in each CO2 category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,
Ambal

N. Ambalavanan MD
Division of Neonatology,
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Tel Office (205) 934 4680 *Lab (205) 934 0751 or 996 5419*
Fax Office (205) 934-3100 *Lab (205) 996 2333*
Email ambal@uab.edu

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 22, 2010 2:48 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,
I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.
Thanks and have a great weekend.
Lisa

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Wednesday, October 20, 2010 10:58 AM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.
Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wed 10/20/2010 9:42 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Ambal,
Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to

cap the amount of time that on CO2 level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.
Thanks.
Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

-----Original Message-----
From: Gantz, Marie <mgantz@rti.org>
Sent: Tuesday, October 19, 2010 7:29 PM
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>
Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>
Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5
75th 12
90th 21
95th 25.5
99th 80
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,
Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Friday, October 15, 2010 2:56 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: RE: PAS ABSTRACT

Hi Lisa,
Thank you for the email.
1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
2) I think PROM>24h is ok
3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.
Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 15, 2010 1:46 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Das, Abhik; Gantz, Marie; Wally Carlo, M.D.
Subject: FW: PAS ABSTRACT

Hi Ambal.
I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted C02 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95th %ile is 25.1 hours and the 99th%ile is 79.8

hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.
I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,
Lisa

From: Wrage, Lisa Ann
Sent: Tuesday, October 05, 2010 2:45 PM
To: 'Namasivayam Ambalavanan'; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:
1) create the CO2 variables of interest and get the rest of the necessary analysis data together
2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.
Lisa

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Tuesday, October 05, 2010 2:38 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,

My answers (>>) are below your questions (**)

Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, October 05, 2010 12:36 PM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Ambal,
Thank you, this is helpful, I have a few more questions (see ** below).
Lisa

From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Tuesday, October 05, 2010 12:42 PM
To: Wrage, Lisa Ann; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Lisa,
(Abhik/Wally/Marie – your comments are also welcome)
If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

***Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.*

>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices

2) For Aim (1): determine the association of PaCO2 in the first 2 weeks with outcomes, we will use PaCO2 as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

***Could you please clarify how you like to summarize PaCO2 over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?*

>> I think max, min, time-weighted, and standard deviation should be ok.

3) For Aims (2) and (3), to determine the association of high/low PaCO2 with outcomes, we will divide infants into quartiles based on their maximum PCO2 and their minimum PCO2 over the first two weeks. The infants in the highest quartile of max PCO2 are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO2 will be the "hypocapnic" ones, and we can also identify a

threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO2 and minimum PCO2. The outcomes will be assessed in the low and high SpO2 groups in relation to PaCO2 status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PC02),* ***>> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators].
Hypocapnic (in lower quartile of min PC02,>> ***Yes. As above, I think we should have hypocapnia only, not fluctuators.***
Fluctuators (in both upper quartile of max PCC02 lower quartile of min PC02)>> ***Yes.***
Normocapnic (in middle two quartiles of max PC02 ***AND*** *min PCC02)*

To define Max PC02 and Min PC02 do you simply want me to use the maximum and minimum value of all values of PC02 for each infant using PC02 recorded during the 1st two weeks on the SUPP05 form?
>> Yes

4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO2, minPCO2, time-weighted PCO2, and SD of PCO2 as independent continuous variables with SUPPORT group assignment

***OK.*
*>>**Great!***

Thanks,
Ambal

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, October 05, 2010 10:32 AM
To: Namasivayam Ambalavanan; ambal@uab.edu
Cc: Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: PAS ABSTRACT

Hi Dr. Ambalavanan,
I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low C02 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus

death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,
Lisa

Lisa Wrage, MPH
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From: Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]
Sent: Friday, October 01, 2010 11:14 AM
To: Das, Abhik; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Hi Lisa, Marie,
What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?
Ambal

N. Ambalavanan MD
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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, September 21, 2010 3:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; ambal@uab.edu
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 21, 2010 11:15 AM
To: Ambal (ambal@uab.edu)
Cc: Wally Carlo, M.D.; Das, Abhik
Subject: PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. You abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.

November 8, 2010– Final abstracts to NICHD for clearance
Mid-November– PAS deadline
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks
Rose

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Title:

Association of $PaCO_2$ with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Authors:

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Short Title: $PaCO_2$ and IVH

Abbreviations: BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

Keywords: Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

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Funding source: Supported by grants from the National Institute of Child Health and Human Development and the Department of Health and Human Services with co-funding from the National Heart, Lung, and Blood Institute (NHLBI) (U10 HD21364, U10 HD21373, U10 HD21385, U10 HD21397, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27871, U10 HD27880, U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40461, U10 HD40492, U10 HD40498, U10 HD40521, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD53119, U10 HD53124) and from the National Institutes of Health (M01 RR30, M01 RR32, M01 RR39, M01 RR44, M01 RR54, M01 RR59, M01 RR64, M01 RR70, M01 RR80, M01 RR125, M01 RR633,

M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

Conflicts of interest: The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

Word count: abstract: 249; text of manuscript: 3106 (Introduction, Methods, Results, and Discussion).

What's known on this subject: Variations in arterial partial pressure of carbon dioxide ($PaCO_2$) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

What this study adds: Higher $PaCO_2$ and greater fluctuation in $PaCO_2$ were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. The correlation of $PaCO_2$ with FiO_2 and days of ventilation support higher maximum $PaCO_2$ as a marker of illness severity

ABSTRACT:

Objective: To determine the association of $PaCO_2$ with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO_2 targets of 85-89% vs 91-95%) and ventilation strategies. Five $PaCO_2$ variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max $PaCO_2$], hypocapnic [lowest quartile of Min $PaCO_2$], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min $PaCO_2$]). Adjusted and unadjusted analyses compared $PaCO_2$ variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max $PaCO_2$ with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all $p < 0.0001$). A higher time-weighted $PaCO_2$ was associated with sIVH/death only if the SpO_2 was lower, and fluctuators were at higher risk for BPD/death only in the higher SpO_2 target group. Max $PaCO_2$ was positively correlated with maximum FiO_2 ($r_s 0.55$, $p<0.0001$) & ventilator days ($r_s 0.61$, $p<0.0001$). **Conclusions:** Higher $PaCO_2$ was associated with sIVH, BPD, and NDI (+/- death). Correlation of $PaCO_2$ with FiO_2 and ventilator days supports higher Max $PaCO_2$ as a marker of illness severity.

(Abstract Word Count = 249)

MANUSCRIPT TEXT

INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ($PaCO_2$) are associated with and may possibly contribute to several important clinical outcomes of prematurity such as intraventricular hemorrhage (IVH)[1], periventricular leukomalacia (PVL)[2, 3], bronchopulmonary dysplasia (BPD)[4], and subsequent neurodevelopmental impairment (NDI)[5]. Increased $PaCO_2$ increases cerebral blood flow,[6-8] while decreased $PaCO_2$ reduces cerebral blood flow, increases cerebral fractional oxygen extraction, and decreases cerebral electrical activity.[9] We have previously shown that both high and low $PaCO_2$ levels and wide fluctuations in $PaCO_2$ are associated with a higher risk of severe IVH (sIVH; IVH Grades III or IV).[1] Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.[2, 3, 10]

Cerebral blood flow decreases slightly with increased oxygenation[8] but the interactions between $PaCO_2$ and oxygenation have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher $PaCO_2$[4, 11, 12] as well as a lower oxygen saturation target,[13] permitting earlier weaning from mechanical ventilation and reduced volutrauma. The combination of a higher $PaCO_2$ (permissive hypercapnia) as well as a lower PaO_2 (targeting a lower SpO_2 range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower oxygen saturation target alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants $24^{0/7}$ to $27^{6/7}$ weeks gestation and compared outcomes in infants randomly assigned to oxygen saturation targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a $PaCO_2$>65 mm Hg permitted intubation, while a $PaCO_2$<65 mm Hg with a pH>7.20 was a mandatory extubation criterion) or intubation and surfactant within 1

hour after birth (a $PaCO_2$<50 mm Hg with a pH>7.30 was a mandatory extubation criterion).[13, 14] Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP (higher $PaCO_2$ target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by day 7 after birth. Between the oxygenation target groups, death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs. 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001), without significant differences in other outcomes although a trend for a reduction in BPD (physiological definition)[15, 16] by 36 wk was noted in the lower saturation target group (38% vs. 41.7%; RR 0.92; CI 0.81, 1.05).[13] There were no significant differences in the composite outcome of death or neurodevelopmental impairment (NDI) among infants in any of the treatment groups.[17]

It is possible that clinical outcomes that are not significantly different by SpO_2 target groups might be different when the combination of $PaCO_2$ and SpO_2 is analyzed. We hypothesized that both extremes of $PaCO_2$ would be associated with severe IVH, and that effect modification of SpO_2 will be observed, with hypercapnia associated with sIVH in the low but not high SpO_2 group. We also hypothesized that BPD would be lower in infants with hypercapnia and low SpO_2, and that higher $PaCO_2$ will be associated with a higher risk of NDI.

PATIENTS AND METHODS

Patient characteristics:

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.[13, 14] Neonatal information collected for the SUPPORT trial included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical outcomes, and treatment. The baseline characteristics of this population[13] and characteristics of the follow-up cohort[17] have been previously reported.

$PaCO_2$ variables

Five $PaCO_2$ variables were defined for this observational study, using routine clinical blood gas measurements that were not governed by study protocol. Data were collected on all $PaCO_2$ from blood gases done at 3 daily time points (maximum) closest to 8 am, 4pm, and midnight on postnatal days 1-14: minimum level, maximum level (Max $PaCO_2$), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted $PaCO_2$ was calculated as described previously.[1] Time between blood gases was capped at 24 hours (~5% of all time difference measurements) so any one blood gas represents no more than 24 hours of time. The median (mean; 5^{th}-95^{th} centiles) of number of blood gases on study day 1 per infant was 2 (2, 1-3), 3 (2.4, 1-3) on study day 3, 2 (2.1, 1-3) on study day 7, and 2 (2, 1-3) on study day 14. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum $PaCO_2$ levels over days 1-14 into quartiles. Infants with minimum $PaCO_2$ levels in the lowest quartile who were not also in the highest quartile of maximum $PaCO_2$ level were then categorized as 'hypocapnic'. Infants with maximum $PaCO_2$ levels in the highest quartile who were not also in the lowest quartile of minimum $PaCO_2$ level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum $PaCO_2$ and the highest quartile of maximum $PaCO_2$ were categorized as 'fluctuators', and the remaining infants, those whose minimum

$PaCO_2$ level fall in quartiles 2-4 and maximum $PaCO_2$ levels fall in quartiles 1-3 were categorized as 'normocapnic'.

Other variables

Maternal hypertension was defined as pregnancy induced hypertension. Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum FiO_2 was defined as the maximum of FiO_2 at 24 hours, day 3, 7, 14 and severe illness was defined *a priori* as FiO_2 >0.4 and mechanical ventilation for 8+ hours in the 1st 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),[18] and BPD was defined using the physiologic definition at 36 w PMA.[15, 16] Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.[17]

Statistical Analysis

The $PaCO_2$ and other variables were compared by each of 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the $PaCO_2$ and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance ($p<.05$) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the Max $PaCO_2$, the 4 level $PaCO_2$ categorical variable, as well as time-weighted $PaCO_2$ were obtained using generalized estimating equation (GEE) models for the binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for the fact that multiple births were randomized to the same treatment arm in the SUPPORT trial. Variables included in the models along with the $PaCO_2$ variable were: birth weight, GA group, gender, race, prenatal steroid use, pregnancy induced hypertension, rupture of membranes>24 hours, and center. SUPPORT trial treatment group variables (High/Low SpO2; CPAP/ventilator) variables were also included in the model that contained Max $PaCO_2$ and the model that contained the 4 level $PaCO_2$ variable. Interactions of these $PaCO_2$ and treatment group variables were also included to assess if the effect of PaCO2 varied by treatment group. A variable for actual median SpO2 in the first 14 days was included in the model that contained time-weighted PaCO2. The interaction of these two variables was included to assess if the effect of time-weighted $PaCO_2$ varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

RESULTS

Adjusted analysis for Severe IVH/Death (**Table 1**):

Max $PaCO_2$ was significantly associated with higher odds of sIVH/death (OR 1.39, 95% CI 1.27-1.53 for an increase in Max $PaCO_2$ of 10 mmHg, $p < 0.0001$). No interaction was found between $PaCO_2$ category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (High or Low SpO_2), but the interaction term for time-weighted $PaCO_2$ and median SpO_2 in the first 14 days was significant ($p<0.05$), with a higher OR associated with a lower median SpO_2 (OR of 1.6 for median SpO_2 of 91, 1.44 for SpO_2 of 92, 1.30 for SpO_2 of 93, 1.18 for SpO_2

of 94) indicating that a higher average $PaCO_2$ was associated with severe IVH/death only if the SpO_2 was lower. Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (the reference group) or hypocapnic infants.

Other variables significantly associated ($p<0.05$) with sIVH/death included: lower birth weight and gestational age, male gender, pregnancy induced hypertension, and center.

Adjusted analysis for BPD/Death (**Table 2**):

Max $PaCO_2$ (OR 1.57, 95% CI 1.41-1.75 for an increase in Max $PaCO_2$ of 10 mmHg, $p < 0.0001$) and time-weighted $PaCO_2$ (OR 2.41, 95% CI 1.89-3.09 for an increase in time-weighted $PaCO_2$ of 10 mmHg, $p < 0.0001$) were significantly associated with higher odds of BPD/death. The interaction term between $PaCO_2$ category and treatment group (High or Low SpO_2) was significant for fluctuators ($p=0.006$), with the OR for fluctuators in the High SpO_2 group being 7.4, as compared to 1.18 for the low SpO_2 group.

Other variables significantly associated ($p<0.05$) with BPD/death included: lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (**Table 3**):

Max $PaCO_2$ (OR 1.38, 95% CI 1.25-1.52 for an increase in Max $PaCO_2$ of 10 mmHg, $p<.0001$) and time-weighted $PaCO_2$ (OR 1.44, 95% CI 1.09-1.90 for an increase in time-weighted $PaCO_2$ of 10 mmHg, $p < 0.0001$) were significantly associated with higher odds of NDI/death. No significant interactions were noted between $PaCO_2$ category and treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic infants (the reference group) or hypocapnic infants. Other variables significantly associated ($p<0.05$) with NDI/death included: lower birth weight and gestational age, male gender, PIH, and center.

Adjusted analysis for Death before discharge (**Table 4**):

Max $PaCO_2$ (OR 1.36, 95% CI 1.22-1.51 for an increase in Max $PaCO_2$ of 10 mmHg, $p<.0001$) was significantly associated with higher odds of death before discharge. Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic infants (the reference group) or hypocapnic infants. Other variables significantly associated ($p<0.05$) with death before discharge included: lower birth weight, male gender, PIH, and center.

As higher Max $PaCO_2$ may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher max FiO_2, days of mechanical ventilation, and severe illness), correlations of Max $PaCO_2$ with max FiO_2, days of ventilation, and severe illness (as previously defined) were calculated. Max $PaCO_2$ was positively correlated with both max FiO_2 (Spearman correlation coefficient = 0.55, $p<0.0001$) and days of ventilation (Spearman correlation coefficient = 0.61, $p<0.0001$). There was also a significant difference in $PaCO_2$ level by infants defined as having severe illness (median max $PaCO_2$=78) vs. infants defined as having no severe illness (median max $PaCO_2$=61), $p<0.0001$ by Wilcoxon two sample test.

Unadjusted Results (**Supplemental Tables 1-4**):

All $PaCO_2$ variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with sIVH as compared to those without sIVH. In general, infants who developed sIVH had a lower minimum, higher maximum and greater variation in $PaCO_2$ as compared to those without sIVH. Max $PaCO_2$ demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median Max $PaCO_2$ between infants with sIVH and those without sIVH. The magnitude of separation in

minimum, standard deviation, and time-weighted $PaCO_2$ were statistically highly significant ($p<0.0001$) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted $PaCO_2$ compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to those for severe IVH and severe IVH or death.

DISCUSSION

We found that extremes of $PaCO_2$ were associated with worse outcome (sIVH, BPD, and NDI) in extremely preterm infants. A higher maximum $PaCO_2$ in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO_2, days of ventilation, and severe illness). A higher average $PaCO_2$ was associated with severe IVH/death only if the SpO_2 was lower. Greater fluctuation in $PaCO_2$ was associated with BPD/death only in the high SpO_2 and not in the low SpO_2 group.

Our study has the limitation that infants in the SUPPORT trial[13, 14] were not primarily randomized to different specific $PaCO_2$ ranges as in the randomized trials of permissive hypercapnia[4, 12, 19] but to interventions (Early CPAP vs. intubation/surfactant) with different $PaCO_2$ goals. Data on corresponding ventilator settings, mean airway pressure, oxygenation index, and ventilation index are not available to determine if reduction of $PaCO_2$ using higher ventilator settings was associated with better outcome in the SUPPORT trial. This study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria for intubation and extubation were used in the trial, and trained research coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Longer-term follow-up was achieved in the majority of infants, and was done

by certified trained personnel. No interaction was observed between maximum $PaCO_2$ and SpO_2 groups, probably because randomization in this trial most likely led to a similar range of $PaCO_2$ in both SpO_2 groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in $PaCO_2$ secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.[14]

Previously, we have shown in a single-center retrospective analysis that both high and low $PaCO_2$ levels and wide fluctuations in $PaCO_2$ are associated with an increased risk of sIVH.[1] The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of $PaCO_2$ were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum $PaCO_2$. As maximum $PaCO_2$ was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum $PaCO_2$ had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average $PaCO_2$ in combination with a lower SpO_2 being associated with severe IVH/death, suggesting that these infants were sicker with greater gas exchange difficulty.

In this cohort, the average (time-weighted) $PaCO_2$ even in infants without severe IVH was $\geq$48 mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the "permissive hypercapnia" range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.[12] Our data indicate clinical practices in academic centers have evolved to maintain $PaCO_2$ in the permissive hypercapnia range. However, as the maximum $PaCO_2$ exceeded this range even in infants without severe IVH, it is apparent that tight control of $PaCO_2$ within this narrow range is difficult.

A higher maximum and time-weighted $PaCO_2$ and a greater magnitude of fluctuation in $PaCO_2$ were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher $PaCO_2$ rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO_2 elimination for a given minute ventilation, due to a higher CO_2 in alveolar air (P_ACO_2). Also, due to the Bohr effect, hemoglobin affinity for oxygen decreases with increasing $PaCO_2$, and peripheral unloading of oxygen improves with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in weaning preterm infants from the ventilator. There is also evidence that hypercapnic acidosis may attenuate ventilator-induced lung injury and inflammation by multiple molecular mechanisms.[9, 11, 14] However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.[4, 11, 12, 19] In the largest randomized trial of permissive hypercapnia to date, which was terminated early due to unanticipated non-respiratory adverse events secondary to dexamethasone therapy, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), despite ventilator support at 36 weeks being 1% in the minimal versus 16% in the routine group ($p<0.01$).[4] An interesting finding was that greater fluctuation in $PaCO_2$ was associated with BPD/death only in the high SpO_2 but not in the low SpO_2 group. It is speculated that higher oxygen exposure in the high SpO_2 group may interact with volutrauma/atelectrauma associated with fluctuating $PaCO_2$ possibly increasing the risk for BPD/death.

Max $PaCO_2$ was also significantly associated with higher NDI/death, confirming our previous single-center study.[5] This association may be secondary to Max $PaCO_2$ being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.[20] Alterations in $PaCO_2$ may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in $PaCO_2$[6-8] may result in sIVH[1] and contribute to NDI. A reduction in cerebral blood flow due to decreased $PaCO_2$[9] may contribute to lower white matter perfusion and result in periventricular leukomalacia (PVL).[2, 3, 10] The brain injury associated with extremes of $PaCO_2$ may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.[21, 22]

In conclusion, our work demonstrates that Max $PaCO_2$ is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO_2, Max $PaCO_2$ may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of $PaCO_2$ with outcomes at later time points and in other populations needs to be determined.

ACKNOWLEDGEMENTS

The National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network's Generic Database Study and Follow-up Study.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Lisa Wrage (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators participated in this study:

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Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

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Table 1: Adjusted results for $PaCO_2$ variables in relation to outcome of severe IVH/death

$PaCO_2$ Variable	**Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.39 (1.27-1.53)	<.0001
$PaCO_2$ Category:		
Hypocapnic	1.11 (0.73-1.67)	0.63
Hypercapnic	2.60 (1.77-3.82)	<.0001
Fluctuator	2.81 (1.68-4.72)	<.0001
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)**		
Median SpO_2=91	1.60 (1.17-2.17)	.0028
Median SpO_2=94	1.18 (0.85-1.62)	0.32

** interaction term for time-weighted $PaCO_2$ x Median SpO_2 in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted $PaCO_2$ depended on level of Median SpO_2.

Table 2: Adjusted results for $PaCO_2$ variables in relation to outcome of BPD/death

$PaCO_2$ Variable	**Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.57 (1.41-1.75)	<.0001
$PaCO_2$ Category:	**High SpO_2**	
Hypocapnic	0.73 (0.46-1.16)	0.18
Hypercapnic	2.54 (1.41-4.60)	0.0019
Fluctuator	7.4 (2.6-21.0)	0.0002
Normocapnic	REFERENCE	-
	Low SpO_2	
Hypocapnic	1.01 (0.63-1.63)	0.96
Hypercapnic	3.38 (1.93-5.93)	<.0001
Fluctuator	1.18 (0.51-2.70)	0.70
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	2.41 (1.89-3.09)	<.0001

** interaction term for $PaCO_2$ category x treatment group (High or Low SpO_2) was significant for Fluctuators

Table 3: Adjusted results for $PaCO_2$ variables in relation to outcome of NDI/death

$PaCO_2$ Variable	**Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.38 (1.25-1.52)	<.0001
$PaCO_2$ Category:		
Hypocapnic	1.03 (0.69-1.53)	0.90
Hypercapnic	2.69 (1.82-3.96)	<.0001
Fluctuator	3.07 (1.84-5.12)	<.0001
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	1.44 (1.09-1.90)	.0093

Table 4: Adjusted results for $PaCO_2$ variables in relation to outcome of death before discharge

$PaCO_2$ Variable	**Odds Ratio (95% CI)**	**p-value**
Max $PaCO_2$ (per 10 mm Hg)	1.36 (1.22-1.51)	<.0001
$PaCO_2$ Category:		
Hypocapnic	0.90 (0.54-1.50)	0. 0.70
Hypercapnic	2.47 (1.61-3.77)	<.0001
Fluctuator	1.88 (1.03-3.43)	.0391
Normocapnic	REFERENCE	-
Time weighted $PaCO_2$ (per 10 mm Hg)	1.28 (0.94-1.74)	0.12

Supplemental Tables

Supplemental Tables:

Table 1- Bivariate analyses for Severe IVH, and for Death or Severe IVH

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
$PaCO_2$, minimum level	#	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	Median, IQR	32 (27-37)	34 (29-38)	.0047	33 (28-38)	34 (30-38)	.69
$PaCO_2$, maximum level	#	163	1098		325	971	
	Mean (SD)	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
	Median, IQR	75 (63-85)	65.5 (55-75)	<.0001	76 (65-88)	64 (54-74)	<.0001
$PaCO_2$, standard deviation	#	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<.0001
$PaCO_2$, time-weighted	#	163	1098		325	971	
	Mean (SD)	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
	Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	.0088	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<.0001
$PaCO_2$ category:	#	163	1098		325	971	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	 30 (18.4) 42 (25.8) 26 (16.0) 65(39.9)	 205 (18.7) 168 (15.3) 70 (6.4) 655 (59.7)	<.0001	 48 (14.8) 102 (31.4) 45 (13.9) 130 (40.0)	 189 (19.5) 127 (13.1) 52 (5.4) 603 (62.1)	<.0001
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	.13	166 (49.6)	496 (50.7)	.73
Treatment: SpO_2 group, High or Low O_2	#	164	1106		335	979	
	High O2, # (%)	81 (49.4)	559 (50.5)	.78	156 (46.6)	505 (51.6)	.11
Median SpO2 DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<.0001
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	.03	750 (640-881)	850 (710-990)	<.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	.08	197 (58.8)	514 (52.5)	.046
Race: NH Black NH White Hispanic Other	# (%)	 55 (33.5) 55 (33.5) 44 (26.8) 10 (6.1)	 421 (38.1) 442 (40.0) 208 (18.8) 35 (3.2)	.016	 112 (33.4) 133 (39.7) 72 (21.5) 18 (5.4)	 376 (38.4) 387 (39.5) 187 (19.1) 29 (3.0)	.092

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value[1]	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value[1]
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	.26	112 (33.4)	376 (38.4)	.104
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	.12	133 (39.7)	387 (39.5)	.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	.03	21 (6.6)	110 (12.0)	.0078
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	.006	97 (30.4)	336 (34.9)	.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	.84	325 (97.3)	938 (95.8)	.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	.022	120 (35.9)	200 (20.4)	<.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	.04	29 (8.7)	29 (3.0)	<.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	.47	117 (37.9)	384 (39.2)	.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	.69	108 (32.2)	325 (33.2)	.74

[1] p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
$PaCO_2$, minimum level	#	441	659		639	659	
	Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
	Median, IQR	33 (29-37)	34 (30-38)	.015	33 (29-38)	34 (30-38)	.25
$PaCO_2$, maximum level	#	441	659		639	659	
	Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
	Median, IQR	72 (64-83)	60 (50-69)	<.0001	73 (65-85)	60 (50-69)	<.0001
$PaCO_2$, standard deviation	#	438	642		625	642	
	Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
	Median, IQR	9.8 (7.8-11.8)	8.0(5.7-9.9)	<.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<.0001
$PaCO_2$, time-weighted	#	441	659		639	659	
	Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
	Median, IQR	51 (47.3-54.3)	46.2 (41.1-50.4)	<.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<.0001
$PaCO_2$ category:	#	441	659		639	659	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	78 (17.7) 101 (22.9) 48 (10.9) 214 (46.5)	138 (20.9) 59 (9.0) 24 (3.6) 438 (66.5)	<.0001	100 (15.7) 170 (26.6) 74 (11.6) 295 (46.2)	138 (20.9) 59 (9) 24 (3.6) 438 (66.5)	<.0001
Treatment: CPAP or Surfactant group	#	442	666		650	666	
	CPAP, # (%)	223 (50.4)	346 (52)	.62	317 (48.8)	346 (52.0)	.25

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
Treatment: SpO_2 group, High or Low O_2	#	442	666		650	666	
	High O2, # (%)	237 (53.6)	331 (49.7)	.20	331 (50.9)	331 (49.7)	.66
Median SpO2 DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<.0001
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<.0001	740 (643-870)	900 (770-1020)	<.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	.043	375 (57.7)	337 (50.6)	.0098
Race: NH Black NH White Hispanic Other	# (%) 157 (35.5) 200 (45.3) 73 (16.5) 12 (2.7)	 268 (40.2) 237 (35.6) 137 (20.6) 24 (3.6)	.013	 221 (34) 284 (43.7) 122 (18.8) 23 (3.5)	 268 (40.2) 237 (35.6) 137 (20.6) 24 (3.6)	.024
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	.11	221 (34)	268 (40.2)	.019
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	.0013	284 (43.7)	237 (35.6)	.0026
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	.18	68 (11.1)	63 (10.1)	.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	.22
Prenatal steroids	#	442	666		649	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p-value[1]	Death or BPD (N=650)	No Death or BPD (N=666)	p-value[1]
	Yes, # (%)	427 (96.6)	636 (95.5)	.36	629 (96.9)	636 (95.5)	.18
1 minute Apgar < 3	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<.0001	207 (31.9)	114 (17.1)	<.0001
5 minute Apgar < 3	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	.11	41 (6.3)	17 (2.6)	.0009
Prophylactic indomethacin	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	.75	240 (38.5)	261 (39.2)	.79
Vaginal delivery	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240(36.0)	.0044	193 (29.7)	240 (36.0)	.014

[1] p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
$PaCO_2$, minimum level	#	98	872		346	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	.0013	33 (28-38)	33 (30-38)	0.95
$PaCO_2$, maximum level	#	98	872		346	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)	
	Median, IQR	74 (65-88)	64 (54-74)	<.0001	76 (66-88)	64 (54-74)	<.0001
$PaCO_2$, standard deviation	#	98	853		335	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<.0001
$PaCO_2$, time-weighted	#	98	872		346	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	.0014	51.7 (47.1-56)	48 (42.8-52.3)	<.0001
$PaCO_2$ category:	#	98	872		346	872	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	22 (22.5) 25 (25.5) 17 (17.4) 34 (34.7)	171 (19.6) 111 (12.7) 44 (5.1) 546 (62.6)	<.0001	51 (14.7) 111 (32.1) 49 (14.2) 135 (39.0)	171 (19.6) 111 (12.7) 44 (5.1) 546 (62.6)	<.0001
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
Treatment: SpO_2 group, High or Low O_2	#	98	878		356	878	
	High O2, # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO2 DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92-94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<.0001	734 (621-870)	850 (710-995)	<.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	.013
Race: NH Black NH White Hispanic Other	# (%)	 37 (37.8) 37 (37.8) 21 (21.4) 3 (3.1)	 333 (37.9) 354 (40.3) 161 (18.3) 30 (3.4)	0.89	 125 (35.1) 139 (39) 78 (21.9) 14 (3.9)	 333 (37.9) 354 (40.3) 161 (18.3) 30 (3.4)	0.47
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
HTN, pregnancy induced	#	88	829		335	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	
	Yes, # (%)	26 (26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

Characteristic		NDI (N= 98)	No NDI (N= 878)	p-value[1]	Death or NDI (N=356)	No Death or NDI (N=878)	p-value[1]
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	.0003	130 (36.6)	181 (20.6)	<.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	.037	29 (8.2)	27 (3.1)	.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	98	878		356	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

[1] p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4 Bivariate analyses for Death

Characteristic		Death (N=237)	No Death (N=997)	p-value[1]
$PaCO_2$, minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	.026
$PaCO_2$, maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<.0001
$PaCO_2$, standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<.0001
$PaCO_2$, time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<.0001
$PaCO_2$ category:	#	227	991	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	26 (11.5) 82 (36.1) 29 (12.8) 90 (39.7)	196 (19.8) 140 (14.1) 64 (6.5) 591 (59.6)	<.0001
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO_2 group, High or Low O_2	#	237	997	
	High O2, # (%)	107 (45.2)	515 (51.7)	.07
Median SpO2 DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<.0001

	Characteristic		Death (N=237)	No Death (N=997)	p-value[1]
	Gender	#	237	997	
		Male, # (%)	144 (60.8)	526 (52.8)	.026
	Race: NH Black NH White Hispanic Other	# (%)	 77(32.5) 96 (40.5) 53 (22.4) 11 (4.6)	 381 (38.2) 397 (39.8) 186 (18.7) 33 (3.3)	0.26
	Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
	Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
	HTN, pregnancy induced	#	226	938	
		Yes, # (%)	16 (7.1)	111 (11.8)	0.04
	Rupture of membranes > 24 hours prior to birth	#	224	980	
		Yes, # (%)	72 (32.1)	332 (33.9)	0.62
	Prenatal steroids	#	236	997	
		Yes, # (%)	7 (3)	41 (4.1)	0.41
	1 minute Apgar < 3	#	236	996	
		Yes, # (%)	90 (38.1)	221 (22.2)	<.0001
	5 minute Apgar < 3	#	237	997	
		Yes, # (%)	22 (9.3)	34 (3.4)	<.0001
	Prophylactic indomethacin	#	211	997	
		Yes, # (%)	83 (39.3)	384 (38.5)	0.82
	Vaginal delivery	#	237	997	
		Yes, # (%)	77 (32.5)	326 (32.7)	0.95

[1] p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

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From: Kennedy, Kathleen A
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu
Subject: ROP Secondary Final Revision
Date: Wednesday, July 03, 2013 8:38:20 AM
Attachments: ROP Natural History Study Manuscript (final revision for J Perinatol, no figures).doc
Figure 2 (revised).pdf
Figure 1 (revised).pdf
Figure 4 (B&W).pdf
Figure 3.pdf

This is the revision after Lisa's changes. I'm going to send it out again to most of the members of the SUPPORT subcommittee because I received very few replies when I sent it before.

Lisa, thanks for working on this. I have one question about the edits you did. There were a lot of formatting changes to the endnote numbers in the body of the manuscript. I couldn't see what you changed and I had to use my version because I had already made some other changes from comments submitted by others. Let me know if it's something important that I need to do on my version.

I also have a question about the number of "severe ROP" outcomes. I was trying to compare this manuscript to the main SUPPORT manuscript so that I could email Wally about the discrepancy created by the error we uncovered. But there is an even bigger discrepancy between the two manuscripts. The primary manuscript has 41+91=132 infants with non-adjudicated severe ROP and this manuscript has 137. Can you explain that?

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
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UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, July 02, 2013 2:21 PM
To: Kennedy, Kathleen A
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Hi Kathleen,
I've attached the updated paper and the two figures that needed to be updated. I noticed a 2 or 3 extra things that I've changed and commented on.
Let me know if you have questions.
I'll be here tomorrow and then out of the office July 4th and 5th.
Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, June 19, 2013 12:31 PM
To: Wrage, Lisa Ann; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thanks for looking into this. I'm glad we got to the bottom of it. I've attached a revision of the manuscript with the changes (in red) that I think we need to make to correct the data error. Nothing important will change but we need to get all the numbers right. There also will be some changes to the figures. I've attached suggested changes (entered as comments on the pdf) for Figure 1. Figure 2 will also have minor changes. I don't think Figures 3 and 4 will look any different, but please verify.

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 19, 2013 9:10 AM
To: Kennedy, Kathleen A; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: FW: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Good Morning,
The Center has replied that the NG03 for this infant is correct: No ROP.
Do you need other information?
Thanks.
Lisa

From: Wrage, Lisa Ann
Sent: Thursday, June 13, 2013 2:47 PM
To: 'Phelps, Dale'; Higgins, Rosemary (NIH/NICHD) [E]; 'Kathleen.A.Kennedy@uth.tmc.edu'
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Our query on this is in process, I'll let you know what we find out.
Thanks.
Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, June 13, 2013 10:10 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Kathleen.A.Kennedy@uth.tmc.edu'; Wrage, Lisa Ann
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Let's see what we learn, and then address this.
I understand the point you are making.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 13, 2013 6:41 AM
To: Phelps, Dale; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'wrage@rti.org'
Cc: 'adas@rti.org'; 'mgantz@rti.org'
Subject: Re: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

The data need to be consistent with the original support report. Probably not worth much more effort for one case.
Rose

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 12, 2013 06:14 PM
To: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Wrage, Lisa Ann <wrage@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik <adas@rti.org>; Gantz, Marie <mgantz@rti.org>
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thanks for brining to my attention Kathleen,
My last phrase was final, but should have had a period instead of 'and', thus ending;
Also, of course, the infant's GDB and SUPPORT paper research files.
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, June 12, 2013 2:54 PM
To: Phelps, Dale; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Dale, it looks like you might have intended to say something else when the last sentence ended.

I agree that this outcome (severe ROP in a 27 wk 1200g infant with no subsequent exams available) is highly improbable. I didn't think we needed the story for this manuscript but now I'm worried that it's an error because it's improbable and inconsistent with what's reported in the GDB for this baby. So I think we need to go to the source documents and try to get to the bottom of it before we publish that there was severe ROP on an initial exam at 33 weeks.

Lisa, the next steps would be figuring out what center and what Network number this is. Then we can go back to the coordinator to try to figure it out. If you need some help with this, please let me know.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 12, 2013 2:20 PM
To: Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thank you very much Lisa,

1. The two figures came out very well without color. Nice work.

2. The clinical narrative for the infant "with severe ROP at first examination at 33 weeks PMA" provides very interesting data. It is a very low probability that this 27 week black female who was not SGA and had minimal complications in the hospital course ever had ROP at all. The GDB data says she did have an examination and that there was no ROP.
   Therefore I strongly suspect that the coding on the ROP data-form for SUPPORT was

an error.
This must be queried.
Can we get paper copies of the ROP exam from the medical record? (HIPAA identifiers blocked out, but Network ID added). Time to go to the source data.
Also, of course, the infant's GDB and SUPPORT paper research files and

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 12, 2013 11:06 AM
To: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Hi, I've attached the updated paper with responses in comments. Dale, I put a short clinical narrative for the baby with severe ROP at first ROP exam in a comment as well. I've also attached updated figures (the colored figures re-done in black/grey/white), Kathleen let me know what you think. I was skeptical about Figure 4 looking ok without color, but to me it appears doable. I should be able to pretty easily change these shades or line styles, if you prefer.
Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Monday, June 10, 2013 6:45 PM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu
Cc: Archer, Stephanie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

I resent this because I previously sent a version of the document that still had old comments. You can ignore those and use this version.

I've made the suggested changes and reformatted this for Journal of Perinatology. The most recent set of changes are in orange text. There are a couple more questions for **Lisa**. If Lisa can easily find the clinical information about the one infant who had severe ROP on the first exam, that would be great (interesting) but I'm not sure we need it for the resubmission. I had to shorten the abstract. They give a page limit (20 including tables and references) for the manuscript instead of a word limit. We're way over, partly because we have 5 pages of acknowledgments and also because each table was supposed to be on a separate page. I hate to take anything out until we figure out what they really want.

Stephanie, the author instructions say that we need to justify having more than 6 authors. I assume that this goes in the cover letter. Do you have any language that we've used successfully for this in the past?

This journal charges ~$1200 for a color figure. That seems ridiculous to me. I thought the $150 per figure in Pediatrics was bad enough. **Lisa**, can you try again to see if we can get the figures into black and white? I think Figure 2 could be done with shades of gray instead of blue. I'm hoping that

figure 4 can be done with different kinds of dashed and dotted lines.

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Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

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Running title: Retinopathy of Prematurity Screening Criteria

Funding source: The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT trial.

Abstract

Objective: To evaluate current retinopathy of prematurity screening guidelines.

Study Design: Data from the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used. Inborn infants 24 $^{0}/_{7}$ to 27 $^{6}/_{7}$ weeks gestational age were enrolled in 2005-2009. Severe retinopathy of prematurity (Type 1 retinopathy of prematurity or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the randomized trial. Examinations followed then current American Academy of Pediatrics screening recommendations.

Results: 997 of the 1121 who survived to first eye exam had final retinopathy of prematurity outcome determined. 137 met criteria for severe retinopathy of prematurity and 128 (93%) of those had sufficient data to determine age of onset of severe retinopathy of prematurity. Postmenstrual age at onset was 32.1 to 53.1 wks. In this referral center cohort, 1.4% developed severe retinopathy of prematurity after discharge.

Conclusion: Our contemporary data support the 2013 screening guidelines. Some infants do not meet treatment criteria until after discharge home.

Keywords (not in title): extremely premature infant

Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines[1],[2] are based on natural history data from the CRYO-ROP[3] and LIGHT-ROP[4] studies. The CRYO-ROP study[5] remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.[6] Over the past two decades, survival of lower birth weight infants in the US and other developed countries has increased.[7,8] For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.[7] The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age.[3] It rarely occurs before 30 weeks postmenstrual age (PMA, sum of GA at birth and chronological age) or before 4 weeks chronological age. Current American Academy of Pediatrics (AAP) recommendations are for screening to begin by 31 weeks PMA for infants born at 22-27 weeks.[1] The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.[4] Based on the results of the ET-ROP trial, treatment is now recommended for Type 1 ROP, defined as stage 3 in zone I or plus disease with any ROP in zone I, or stage 2 or 3 with plus disease in zone II. Since Type 1 ROP occurs earlier in the course than CRYO-ROP threshold ROP, it is important to determine if screening criteria developed for CRYO-ROP threshold ROP are still appropriate for reliable timely

identification of Type 1 ROP.[9] There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial[10] and a population-based cohort study of infants born 2004-2007 in Sweden[11] reported the age of onset of stages 1, 2, and 3 ROP; however, the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from Canada reported the age of onset of Type 1 ROP in a cohort of 214 infants ≤ 27 weeks gestation;[12] this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort[13] reported that "No preterm infants required treatment before the 33rd postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for severe ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 $^{6}/_{7}$ weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)[14] to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O_2 saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants.[14] Inborn infants $24\ ^{0}/_{7}$ – $27\ ^{6}/_{7}$ weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 31-33 weeks postmenstrual age, as recommended in the AAP guidelines in place when the study began.[15,16] Subsequent inpatient and outpatient exams were conducted according to the ophthalmologists' established screening procedures at each center. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Study eye exam data were recorded for each exam until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up (including exams after hospital discharge) was curtailed at 55 wks PMA.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time prior to detection. Infants

with Type 1 ROP whose first exam with Type 1 ROP preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. No infants had Type 1 ROP on the initial exam. Infants who did not complete exams according to the study schedule had ROP outcomes adjudicated by a panel of three ophthalmologists and were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for quantiles.[17] Cumulative incidence curves for age of onset of severe ROP and age of maturity were compared by gestational age subgroups (26-27 weeks vs 24-25 weeks) using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-four percent (643/997) of these infants developed ROP and 14% (137/997) developed severe ROP. Among infants with severe ROP, 93% (128/137) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-

Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for ROP are shown in Table 2.[18,19,20] Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ($p<0.05$ for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3. For the 9 infants with severe ROP and uncertain age of onset, the age of identification ranged from 33.7-40.0 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (low oxygen saturation and high oxygen saturation target) and the distributions were similar so only the combined data are shown. The distributions for age of onset of severe ROP for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to prior studies,[3] our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. PMA of onset of severe ROP is significantly later for GA groups 26-27 weeks vs. 24-25 weeks ($p<0.01$). There is no significant difference in the distribution of chronologic age of onset between these two GA groups.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had

mild or moderate ROP (ROP that did not meet criteria for severe ROP). The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ($p < .0001$).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but there are no risk factors that clearly identify infants at risk to develop severe ROP after discharge.

Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,[9] so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies[3] in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,[3] lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation by the AAP that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,[1] albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight (≤1250 g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.[21] Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, it is likely that the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age[22] and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset

was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,[11] which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al[12] included 23-27 week infants; infants ≤25 weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants >25 weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (24-25 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest ages of onset of Type 1 ROP are more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,[12] the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al[13] that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged

or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study has several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.[23] The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Current AAP screening guidelines, published in 2013,[1] recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines. In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.[23]

Acknowledgments

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; Anna M. Dusick, MD FAAP; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

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Conflict of Interest: The authors declare that they have no financial interests related to the work described in this manuscript.

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Figure Legends:

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all SUPPORT trial infants with known outcome

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP[1] Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/ Moderate ROP	Severe (Type 1 or Treated) ROP
n	1316	997	354	506	137
Gestational age, wks [mean (SD[2])]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.4 (0.9)
Birth weight, g [mean (SD)]	830 (193)	849 (190)	943 (173)	823 (180)	704 (142)
Small for gestational age[3] [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	154 (44)	179 (35)	41 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (45)
Hispanic	259 (20)	190 (19)	69 (19)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (57)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	341 (96)	480 (95)	134 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

[1] Retinopathy of prematurity
[2] Standard deviation
[3] Based on Olsen[24] growth curves

Table 2. Risk factors for ROP[1]

Risk Factor	No ROP	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	354	506	137
Days on supplemental oxygen[2] [median (IQR[3])]	33 (10, 60)	59 (31, 94)	95 (68, 119)
Late-onset sepsis (+ culture) [(n (%)]	75 (21)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	15[4] (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	69[4] (14)	29 (21)
Proven necrotizing enterocolitis[5] [n (%)]	20 (6)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	123 (35)	271 (54)	94 (69)

[1] Retinopathy of prematurity
[2] Tabulated until 120 days or discharge if discharged sooner, among infants who survived to discharge, transfer or 120 days
[3] Interquartile range
[4] Missing data for 1 infant
[5] Modified Bell's stage II or III[25]

Table 3. Postmenstrual and chronological age of onset[1] [with 95% confidence intervals (CI[2])] of any stage ROP[3] (among infants with ROP age of onset determined)

		Postmenstrual Age (weeks)								
ROP type	n	Min[4]	1%	5%	25%	50%	75%	95%	99%	Max[4]
Any ROP (95%CI)	634	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP[5] (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

		Chronological Age (weeks)								
ROP type	n	Min	1%	5%	25%	50%	75%	95%	99%	Max
Any ROP (95%CI)	634	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP[3] (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

(95% CI)										

[1] Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

[2] Confidence interval

[3] Retinopathy of prematurity

[4] Min = minimum age at which designated severity of ROP was identified; max = maximum age.

[5] Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP[1] criteria in relation to discharge and transfer

Infants with Severe ROP N=137	First exam with severe ROP occurred before discharge to home n=123	First exam with severe ROP criteria occurred after discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks [median, range]	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks [median, range]	42.5 (37.7-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital [n]	1	4

[1] Retinopathy of prematurity

Table 5. ROP[1] exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

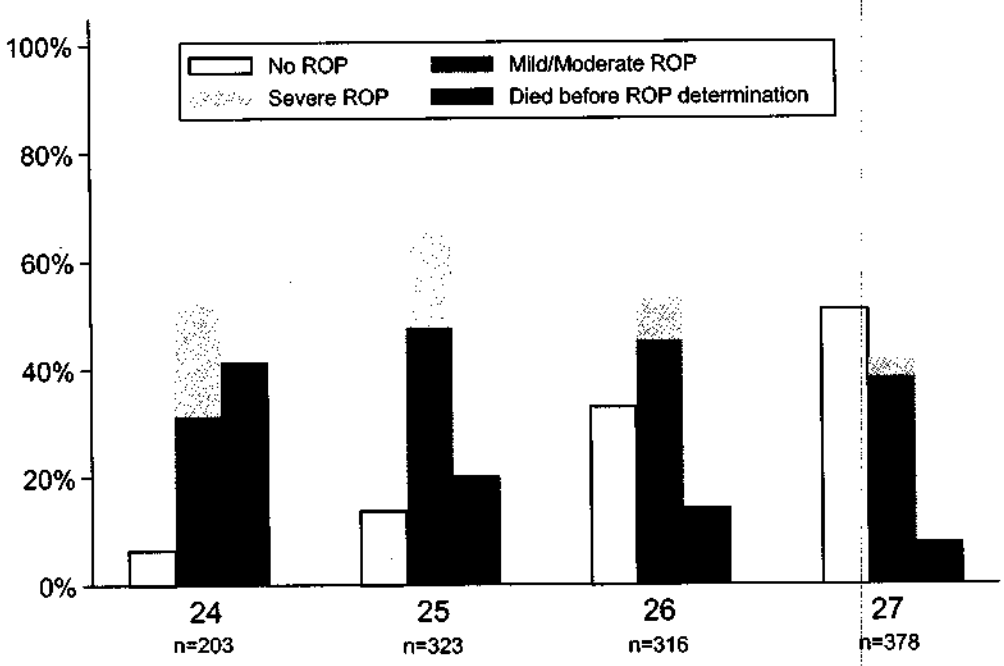
Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I [n (%)]	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone [n (%)]	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP [n (%)]	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone [n (%)]	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP [n (%)]	0	121 (23%)
Plus disease [n (%)]	0	0
No exam prior to discharge [n (%)]	0	3
Unknown (missing or incomplete information on exam prior to discharge) [n (%)]	0	5

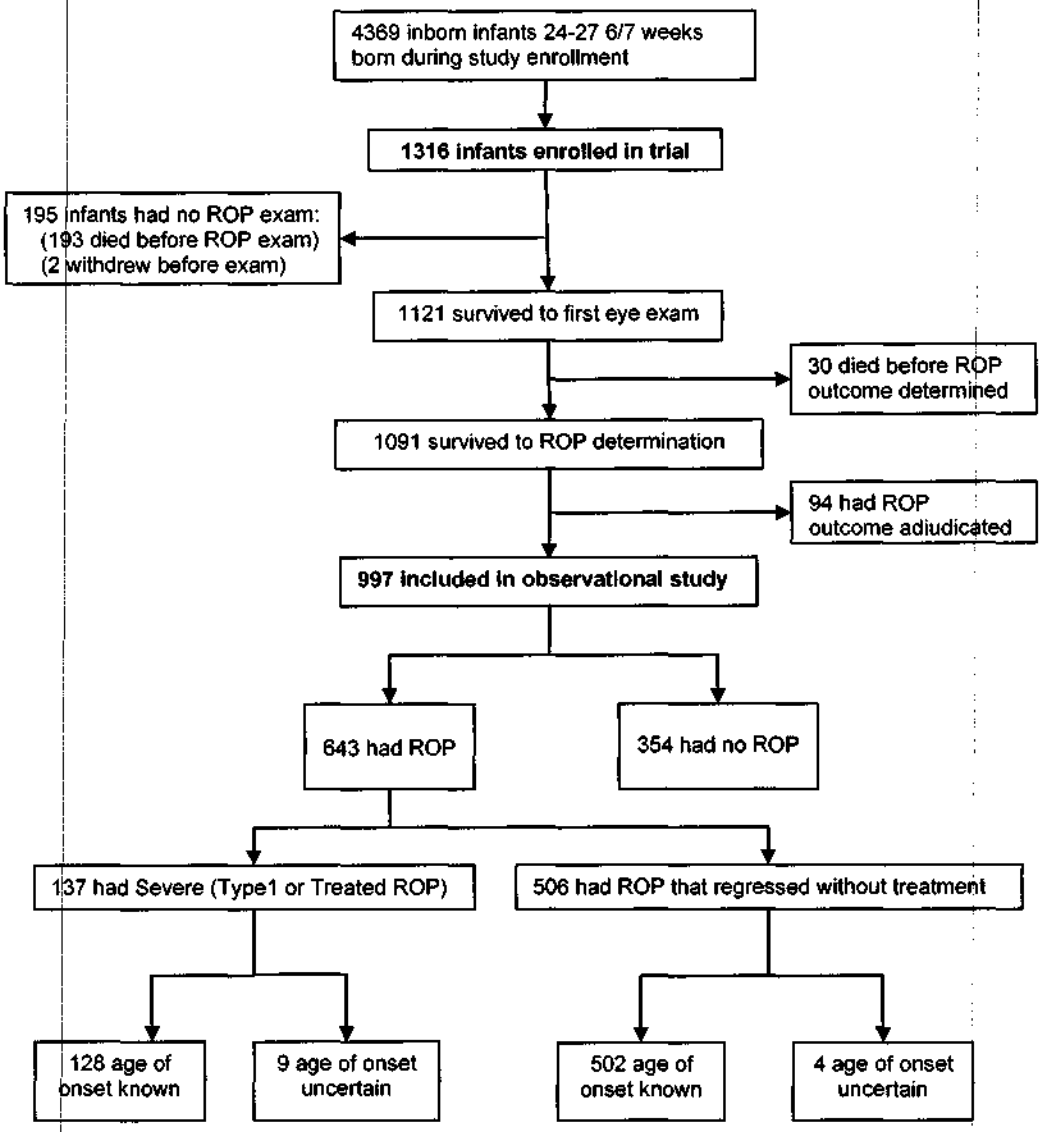
[1] Retinopathy of prematurity

Table 6. Risk factors for ROP[1] for infants with final ROP status determined after discharge home

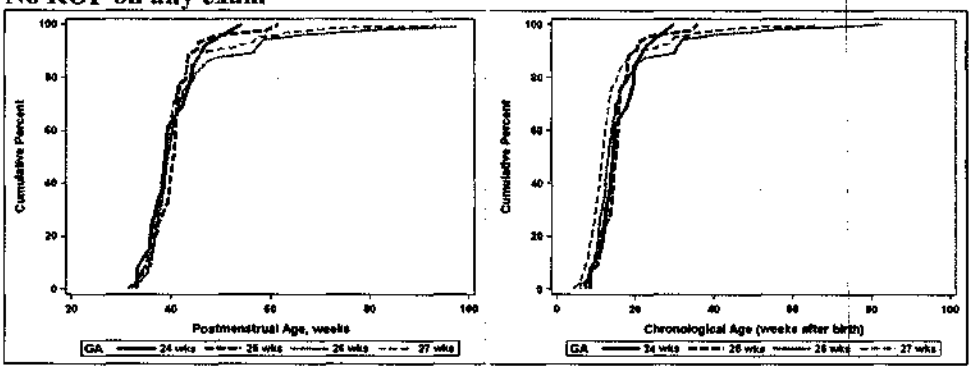
Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, g [mean (SD)]	701 (103)	872 (185)
GA[2] at birth, wks [mean (SD)]	25.7 (0.9)	26.4 (1.0)
Days on oxygen [mean (SD)]	59 (27)	47 (33)
Early onset sepsis [n (%)]	0	10 (2)
Late onset sepsis [n (%)]	7 (50)	148 (28)
Fungal sepsis [n (%)]	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	0	59 (11.1)
Proven necrotizing enterocolitis [n (%)]	1 (7)	36 (7)
Patent ductus arteriosus [n (%)]	11 (79)	258 (48)
Discharge on oxygen [n (%)]	2 (14)	88 (16)

[1] Retinopathy of prematurity
[2] Gestational age

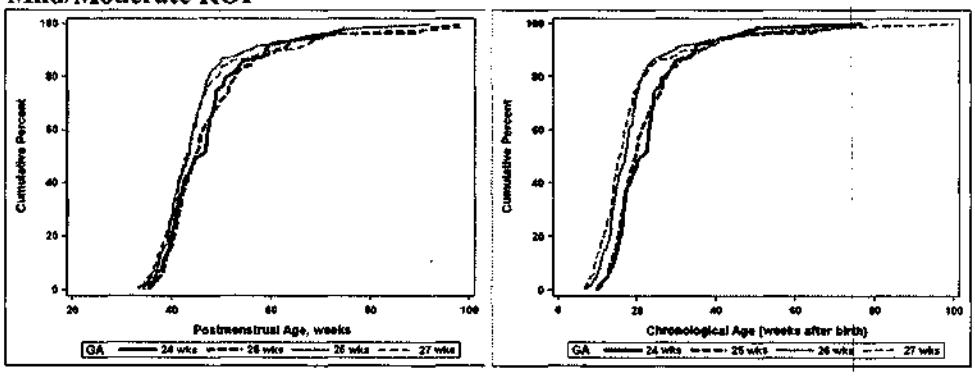


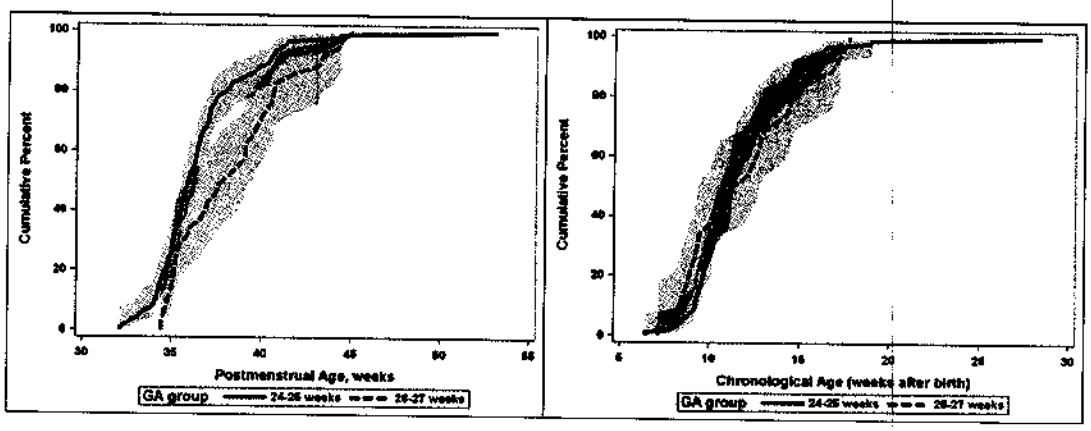


No ROP on any exam



Mild/Moderate ROP





From: Pemberton, Victoria (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: GoTo Training NOT working: alternative log-in RE: SUPPORT Study: CTSA CRE Consultation Working Group call
Date: Tuesday, July 02, 2013 11:35:32 AM
Attachments: image001.png
CRE KFC consult Workgroup 7.2.13agenda..ppt
Importance: High

See link below

Victoria Pemberton, RNC, MS, CCRC
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From: CTSA Child Health [mailto:CTSA_ChildHealth@CTSAC4.Org]
Sent: Tuesday, July 02, 2013 11:22 AM
To: CC-CHOC Listserv (list.cc-choc@ctsacentral.org)
Subject: FW: GoTo Training NOT working: alternative log-in RE: SUPPORT Study: CTSA CRE Consultation Working Group call
Importance: High

Please use the link below for the CRE call on the SUPPORT Study.
If you are only calling in on the phone, I will be sending out a phone number shortly.

Regards,
Cindy

Cindy Pastern, RN BSN | CC-CHOC Project Manager
CTSA Consortium Coordinating Center (C4)
My desk: 615.343.0259| Hotline: 855.514.7001
CTSA_ChildHealth@CTSAC4.org

From: CTSA Ethics
Sent: Tuesday, July 02, 2013 10:13 AM
To: CTSA Ethics; 'list.key.ethics@ctsacentral.org'
Cc: Pastern, Cindy; Swindell, Bridget; Fair, Alecia S; CTSA Inquiry
Subject: GoTo Training NOT working: alternative log-in RE: SUPPORT Study: CTSA CRE Consultation Working Group call

All:
Please use the following link to access the consultation call scheduled at 10:30 CST:
http://www.anymeeting.com/eaglei1

Sincerest apologies for the inconvenience this has caused.

Lisa Robins, D.Psy., MPH, MBA | Project Manager
Clinical Research Ethics Key Function Committee
CTSA Consortium Coordinating Center (C^4)
My desk: 615.343.4929 | Hotline: 855.514.7001
E-mail: CTSA_Ethics@CTSAC4.org

From: CTSA Ethics [mailto:CTSA_Ethics@ctsac4.org]
Sent: Wednesday, June 26, 2013 1:48 PM
To: 'list.key.ethics@ctsacentral.org'
Subject: SUPPORT Study: CTSA CRE Consultation Working Group call

Dear Colleague,

The July 2 quarterly case discussion for the Clinical Research Ethics (CTSA) Consultation Working Group will be based on the SUPPORT Study. The call will take place from 1130-100pm ET. Dr Wally Carlo will kick off the call with a description of the study and the issues that emerged.

Our discussion will focus on 4 topics:

- Evaluating risks of standard practice
- Evaluating risks of research
- Evaluating parental permission
- Improving parental permission

This first three will be more conceptual discussions to raise and explore issues, and the final topic will be more action oriented to gauge interest for a CTSA related project.

Attached are slides with a more detailed agenda.

Because of the broad based interest in this topic, this invitation is being sent to all CRE (ethics) and CC-CHOC(pediatrics) CTSA members. Below are the go to meeting links. Please log-in to use GTT as we hope to use the "raise hands" feature to coordinate the discussion. Looking forward "seeing" you in cyberspace.

Ethics Consultation Workgroup Quarterly Case Conference
Tuesday, July 2, 2013 11:30 AM - 1:00 PM EDT

Audio: Participants can use their computer's microphone and speakers (VoIP) or telephone.
United States
Toll-free: 1 877 739 5904
Toll: +1 (714) 551-5078
Access Code: 809-599-341
Audio PIN: Shown after joining the training
Registration URL: https://student.gototraining.com/r/2243373504663308288

Training ID: 699-940-436

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Lessons from SUPPORT: Improving parental permission in NICU research

July 2, 2013

CRE Consultation Working Quarterly Case Discussion

11:30-1:00 ET

Case Presenter: Wally Carlo MD

University of Alabama

Agenda

- Understanding Support (15 min)
- Discussion
  - Evaluating risks of standard practice (15 min)
  - Evaluating risks of research (15 min)
  - Evaluating parental permission (15 min)
  - Improving parental permission (15 min)

  Wrap up and CRE updates. (15 min)

Understanding SUPPORT

- Describe the state of the science, the rationale for the study, and the views of clinicians about the use of pulse oximetry, when the study was conceived.

- Describe the study design, the primary and secondary end points, and how the level of risk was being imagined by the investigators

- Discuss the consent process used in approaching parents and explaining the study and what worked well and did not.

Evaluating risks of standard practice

- When investigators and clinicians do not agree about the degree of uncertainly about standard care, what are the moral distinctions between providing a standard approach and enrolling infants in a research trial?

Evaluating risks of research

- How should we evaluate the research risks to participants, when comparing standard interventions in a clinical context of high morbidity.

- Should refinements of standard approaches to improve benefits appropriately be considered risks, in the same way that using novel interventions and drugs are?

- Does randomization pose additional risks?

Evaluating Parental Permission

- Is the goal of parental permission to improve understanding and promote decision-making for research participation?

- Do we know what is the best way to get permission from parents for research for prematurely born infants, which is often emergent and stressful?

Improving Parental Permission

- How do we improve written materials and what other interventions might help?
- What role can CTSAs play to improving the approach to parental permission?

From: Archer, Stephanie (NIH/NICHD) [E]
To: "Cunningham, Meg"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Results
Date: Tuesday, July 02, 2013 10:28:44 AM

No restrictions.

NICHD can review communications, but can't restrict them (just refuse to have our name on it). PI's are free to publish what they way as long as it doesn't violate the NRN policies (e.g., publishing before the primary paper is out, etc.).

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, July 02, 2013 10:19 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Results

OK. Then I need to provide answers to the following. Can you let me know how I should answer these.

Results Disclosure Restriction on PI(s)? (Y/N) [*] If there is an agreement between the sponsor (or its agent) and any non-employee PI(s) that restricts the PI's rights to discuss or publish trial results after the trial is completed, select "Yes" and select a "Restriction Type." Trial completion is defined as the final date on which data were collected. (ie, the Study Completion Date from the Protocol Data Elements)

If there are agreements with multiple non-employee PIs and there is a disclosure restriction on at least one PI, select "Yes" and answer the remaining question. If there are varying agreements with PIs, choose the type below that represents the most restrictive of the agreements (e.g., the agreement with the greatest embargo time period).

PI Disclosure Restriction Type : Select one

- The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days** from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.
- The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days** from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.
- Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed

Other Disclosure Restriction Type : If "Other disclosure agreement..." is selected, please describe the type of agreement including any provisions allowing the sponsor to require

changes, ban the communication, or extend an embargo.
(Limit: 500 characters)

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, July 02, 2013 10:17 AM
To: Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Results

None of the PIs are direct employees of NICHD.

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Tuesday, July 02, 2013 10:03 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT Results

Hi Rose,

One question I must answer for results in clinicaltrials.gov is:

Are all PIs Employees of Sponsor? (Y/N) * : If all principal investigators are employees of the sponsor, select "Yes" and skip the remaining questions. If any principal investigator (PI) is not an employee of the sponsor, select "No" and answer the remaining questions.

How should I answer this?
Meg

Blansfield, Earl (NIH/NICHD) [E]

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Tuesday, July 02, 2013 8:44 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: URGENT CLEARANCE DUE BY 2:00 PM TODAY (July 2)- 322943
Attachments: Response to Public Citizen on Natanson - revised.doc

HI – sorry to bother you, but they want clearance by 2 pm. This is the letter that we requested be reassigned (re: SUPPORT). Pretty terse response, but probably what's needed. Do you have any comments on it?

Thanks,

L

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Whitfield, Michelle D. (NIH/OD) [E]
Sent: Tuesday, July 02, 2013 8:36 AM
To: Kaeser, Lisa (NIH/NICHD) [E]
Subject: RE: URGENT CLEARANCE DUE BY 2:00 PM TODAY (July 2)- 322943

Good morning Lisa,

Sure! Here is a copy of the incoming and the response.

Thank you,
Michelle

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Tuesday, July 02, 2013 8:35 AM
To: Whitfield, Michelle D. (NIH/OD) [E]
Subject: RE: URGENT CLEARANCE DUE BY 2:00 PM TODAY (July 2)- 322943

Hi – Sandy is out – can you send to me please?

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH

31 Center Drive, MSC 2425
Building 31, Room 2A03
Bethesda, MD 20892
301-496-0536
kaeserl@mail.nih.gov

From: Whitfield, Michelle D. (NIH/OD) [E]
Sent: Tuesday, July 02, 2013 8:34 AM
To: Ott, Sandra (NIH/NICHD) [E]; Sanchez, Samantha (NIH/OD) [C]
Cc: Kaeser, Lisa (NIH/NICHD) [E]
Subject: URGENT CLEARANCE DUE BY 2:00 PM TODAY (July 2)- 322943
Importance: High

Good morning,

I wanted to give you a heads up- I just sent #322943 to your office for clearance. It is due by 2:00 pm today.

I apologize for the short turnaround.

Thank you,
Michelle

July XX, 2013

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group
1600 20th Street, N.W.
Washington, D.C. 20009

Dear Dr. Carome:

Thank you for your letter dated June 13, 2013, expressing your concern that the NIH declined participation of Dr. Charles Natanson in a webinar in July regarding the SUPPORT study. I appreciate you taking the time to share your views.

One of the goals of the NIH is to promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science. I can assure you that this is a responsibility, and a privilege, that is taken very seriously.

Sincerely,

The Honorable Kathleen Sebelius
Secretary

From: Bradley Yoder
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Question & Update
Date: Monday, July 01, 2013 11:04:03 AM

Please see below; didn't know we had begun to encrypt messages outside U.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Bradley Yoder
Sent: Friday, June 28, 2013 3:25 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Roger Faix
Subject: PHI SUPPORT

Hi Rose, we received a request from a law firm (Leif, Cabraser, Heimann & Bernstein; out of San Francisco) regarding documents related to one of our SUPPORT babies whose parents have initiated at least some pretense to litigation.
One of the items they are requesting is information regarding the oxygen group the infant belonged to.
We know his network #, randomization #, and color of oximeter....but I have no idea which SAT arm he was in.
Is this information that is being released to us if needed?
Has Wally needed this at UAB?

Thanks for your support and response on this.

Brad

Bradley A. Yoder, MD
Professor of Pediatrics
Division of Neonatology
University of Utah School of Medicine
PO Box 581289
Salt Lake City, UT 84158-1289

Phone 801-587-3498
Pager (b)(6)
Email Bradley.yoder@hsc.utah.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bradley Yoder"
Subject: RE: PHI SUPPORT
Date: Monday, July 01, 2013 8:33:52 AM

Brad
I can't open this – either fax it or feel free to call me
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Friday, June 28, 2013 6:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: PHI SUPPORT

You have received a secure message

You are receiving this secure email because it is federally mandated that any personal health information that is electronically provided to patients must be secure.

We at the University of Utah Health Care understand your information is personal and are committed to protecting it.

If you have concerns about the validity of this message, contact the help desk at **801-587-6000** with any questions or comments.

Read your secure message by opening the attachment, securedoc_20130628T222428.html. You will be prompted to open (view) the file or save (download) it to your computer. For best results, save the file first, then open it in a Web browser. To access from a mobile device, forward this message to mobile@res.cisco.com to receive a mobile login URL.

First time users - will need to register after opening the attachment. For step by step instructions, click the following Help link.
Step by Step Help -

From: Bradley Yoder
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: PHI SUPPORT
Date: Friday, June 28, 2013 6:24:32 PM
Attachments: securedoc_20130628T222428.html

You have received a secure message

You are receiving this secure email because it is federally mandated that any personal health information that is electronically provided to patients must be secure.

We at the University of Utah Health Care understand your information is personal and are committed to protecting it.

If you have concerns about the validity of this message, contact the help desk at **801-587-6000** with any questions or comments.

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First time users - will need to register after opening the attachment. For step by step instructions, click the following Help link.
Step by Step Help - http://privacy.utah.edu/_pdf/encrypted-email.pdf

Additional Help, click the following Help link.
Help - https://res.cisco.com/websafe/help?topic=RegEnvelope
About Cisco Registered Email Service - https://res.cisco.com/websafe/about

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, June 27, 2013 5:06 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Lauren (NIH/OD) [E]
Subject: FW: fed reg notice

http://www.gpo.gov/fdsys/pkg/FR-2013-06-26/pdf/2013-15160.pdf.

Wanted to make sure you guys had this.

responsibilities regarding the maintenance and availability of inventory records of assets. Without this information or ability to access the information, after an ownership change, the Government would be unable to ascertain whether contractor assets were properly valuated. The cost principles at FAR 31.205–52 address the allowability of certain costs resulting from asset valuations following business combinations. In order to administer the cost principles adequately, the information required by FAR 52.215–19 is necessary.

Comment: The respondent commented that the agency did not accurately estimate the public burden challenging that the agency's methodology for calculating it is insufficient and inadequate and does not reflect the total burden.

Response: Serious consideration is given, during the open comment period, to all comments received and adjustments are made to the paperwork burden estimate based on reasonable considerations provided by the public. This is evidenced, as the respondent notes, in FAR Case 2007–006 where an adjustment was made from the total preparation hours from three to 60. This change was made considering particularly the hours that would be required for review within the company, prior to release to the Government.

The burden is prepared taking into consideration the necessary criteria in OMB guidance for estimating the paperwork burden put on the entity submitting the information. For example, consideration is given to an entity reviewing instructions; using technology to collect, process, and disclose information; adjusting existing practices to comply with requirements; searching data sources; completing and reviewing the response; and transmitting or disclosing information. The estimated burden hours for a collection are based on an average between the hours that a simple disclosure by a very small business might require and the much higher numbers that might be required for a very complex disclosure by a major corporation. Also, the estimated burden hours should only include projected hours for those actions which a company would not undertake in the normal course of business.

Upon consideration of the respondent's comments and review of Fiscal Year 2012 (FY12) Federal Procurement Data System (FPDS) information an adjustment is being made to the estimated annual burden. Based on FPDS information approximately 1200 novations and non-novated mergers and acquisitions were recorded in FY12 as descriptions for modifications. However, it is estimated that 50 percent or 600 of such actions will require the contractor to meet the requirements specified at FAR 52.215–19. The clause is only required to be inserted in solicitations and contracts for which it is contemplated that certified cost or pricing data will be required or for which any pre-award or post-award cost determination will be subject to *Subpart 31.2.* The estimate of hours per response is adjusted upwards to partly allow for the internal coordination and analysis before submitting the information to the Government as stated by the respondent. However the significant adjustment suggested was not made because, apart from a notification to the ACO, the requirements of the clause are passive, requiring contractors to maintain rather than to create records to meet the specific requirements for Government submission, and should be part of the normal course of doing business. At any point, members of the public may submit comments for further consideration, and are encouraged to provide data to support their request for an adjustment.

C. Annual Reporting Burden

Respondents: 600.

Responses per Respondent: 1.

Total Responses: 600.

Hours per Response: 5.

Total Burden Hours: 3000.

Obtaining Copies of Proposals: Requesters may obtain a copy of the information collection documents from the General Services Administration, Regulatory Secretariat (MVCB), 1275 First Street NE., Washington, DC 20417, telephone (202) 501–4755. Please cite OMB Control No. 9000–0115, Notification of Ownership Changes, in all correspondence.

Dated: June 21, 2013.

William Clark,

Acting Director, Office of Governmentwide Acquisition Policy, Office of Acquisition Policy, Office of Governmentwide Policy.

[FR Doc. 2013–15300 Filed 6–25–13; 8:45 am]

BILLING CODE 6820–EP–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

AGENCY: Office of the Secretary, Department of Health and Human Services.

ACTION: Notice of meeting and request for comments.

SUMMARY: The Department of Health and Human Services (HHS) is announcing a public meeting to seek public input and comment on how certain provisions of the HHS requirements related to the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically is requesting input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. HHS is seeking participation in the meeting and written comments from all interested parties, including, but not limited to, IRB members, IRB staff, institutional officials, research institutions, investigators, research subject advocacy groups, ethicists, and the regulated community at large. This meeting and the written comments are intended to assist HHS, through the Office for Human Research Protections (OHRP), Office of the Assistant Secretary for Health (OASH), in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects. HHS is seeking input on a number of specific questions but is interested in any other pertinent information participants in the public meeting would like to share.

DATES: *Meeting:* The public meeting will be held on August 28, 2013, from 9 a.m. to 5 p.m.

Deadline for Registration for Participants (not Presenting) at the Public Meeting and Submitting Requests for Special Accommodations: Registration to attend the public meeting and requests for special accommodations must be received no later than 5 p.m. on August 14, 2013.

Deadline for Registration of Presenters at the Public Meeting: Registration to present at the public meeting must be received no later than 5 p.m. on August 7, 2013.

Deadline for Submission of Written Comments for the Public Meeting: Written comments for discussion at the public meeting must be received no later than 5 p.m. on August 7, 2013. In addition to materials submitted for discussion at the public meeting, individuals may submit other written comments after the public meeting, as specified in the **ADDRESSES** section of this notice. These comments must be received no later than 5 p.m. on September 9, 2013, for consideration by HHS.

ADDRESSES: The Public Meeting will be held at the Department of Health and Human Services, Hubert H. Humphrey Building, 200 Independence Ave. SW., Great Hall, Washington, DC 20201; Metro: Federal Center SW station.

In addition, we are providing an alternative to attending the meeting in person; participants may view the public meeting via live streaming technology. Information on that option is provided in section II.D. of this notice.

Registration and Special Accommodations: While there is no registration fee, individuals planning to attend the public meeting in person must register to attend. Registration may be completed by sending an email to *OHRP@hhs.gov*, with the subject line "Registration for HHS Public Meeting"; or a request to register may be sent to: Registration for HHS Public Meeting, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852. Please include your name, address, telephone number, email address, and fax number. If you would like to present at the public meeting, please state this in the registration submission.

Registration to attend the public meeting will be accepted on a first-come, first-served basis. If seating capacity has been reached, you will be notified that the meeting has reached capacity.

Registration to present at the public meeting will be accepted on a first-come, first-served basis. HHS has included questions for comment in section III of this document. Please identify by number each question you wish to address in your presentation and the approximate time requested. HHS will do its best to accommodate requests to speak. HHS will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin. Once HHS notifies registered presenters of their scheduled times, presenters should submit a copy of each presentation, identified with docket number HHS–OPHS–2013–0004, to *http://www.regulations.gov*.

Individuals who need special accommodations should contact staff listed in the **FOR FURTHER INFORMATION CONTACT** section of this notice.

Submission of Comments for the Public Meeting

Submit electronic comments, identified with docket number HHS–OPHS–2013–0004, to *http://www.regulations.gov*.

Submit written comments to Comments for HHS Public Meeting, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dr. Jerry Menikoff, Director, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852; phone 240–453–6900; email *Jerry.Menikoff@hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

A. HHS Protection of Human Subjects Regulations

HHS, through OHRP, regulates research involving human subjects conducted or supported by HHS in regulations. The HHS human subjects protection requirements pertain to several different entities, including the IRB charged with reviewing non-exempt human subjects research.

The IRB is an administrative body that takes the form of a board, committee, or group, and is responsible for conducting the initial and continuing review of research involving human subjects. The IRB must have authority to approve, require modification in (in order to secure approval), or disapprove all research activities regulated by HHS. An IRB's primary purpose in reviewing research is to ensure the protection of the rights and welfare of human research subjects. In order to approve research, an IRB is required to make certain determinations, including that the following criterion is met:

> Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

The HHS human subjects protections further require that, unless this requirement is waived by the IRB, an investigator must obtain informed consent from research subjects prior to the subjects' participation in the research, and that, in this informed consent process, the subjects must be provided "a description of any reasonably foreseeable risks or discomforts to the subject."

B. OHRP's Compliance Oversight Investigation of SUPPORT

On March 7, 2013, OHRP issued a compliance oversight determination letter regarding its investigation into "The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" (SUPPORT) clinical trial (*http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf*), in which OHRP determined that certain risks related to the interventions being studied in the SUPPORT trial were required by the HHS protection of human subjects regulations to be disclosed to the research subjects, and the subjects were not informed of these risks. OHRP's view of the SUPPORT trial, as described in this determination letter, triggered extensive public discussions regarding (1) what risks to subjects are presented by clinical trials studying interventions that are standard of care in the clinical treatment context, such that an IRB must evaluate those risks in relation to the anticipated benefits of the research; and (2) how an IRB should assess whether those risks are reasonably foreseeable such that the risks must be described to subjects in informed consent. Through the public reaction to OHRP's determination letter, HHS has become aware of differing perspectives in the scientific, research, and ethics communities about these issues and how the relevant requirements of the HHS protection of human subjects regulations should apply to research studying standard of care interventions.

II. Public Meeting

A. Purpose and Scope of the Meeting

The public meeting is intended to provide an opportunity for broad public participation and comment concerning how the HHS human subjects

protections requirements should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically is requesting input regarding how an IRB should assess the risks of research involving randomization to one of more standard of care interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. This meeting and the written comments are intended to assist HHS, through the OHRP, OASH, in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects.

While HHS is considering whether other processes should be incorporated into OHRP's compliance oversight procedures and guidance, including, but not limited to, consultation with subject matter experts during the course of a compliance oversight investigation, and an administrative process for appealing OHRP determinations of noncompliance, this meeting is not intended to specifically address possible revisions to OHRP's compliance oversight procedures.

B. Format of the Meeting

The meeting will be conducted by a panel of HHS officials, including the Director of OHRP. The majority of the meeting will be reserved for presentations of comments, recommendations, and data from registered presenters. The time for each presenter's comments will be determined by HHS and will be based on the number of registered presenters. Presenters will be scheduled to speak in the order in which they register. Only the HHS panel members may question any presenter during or at the conclusion of each presentation. The meeting will be recorded and transcribed.

In addition, written comments will also be accepted and presented at the meeting, time permitting, if they are received by the date specified in the **DATES** section of this notice.

C. Security and Building Guidelines

Because the public meeting will be located on federal property, for security reasons any persons wishing to attend this meeting must register by the date specified in the **DATES** section of this notice. Attendees should allow sufficient time to go through the security checkpoints. Attendees should arrive at the Hubert H. Humphrey Building no later than 8:30 a.m.

Security measures include the following:

- Presentation of government-issued photographic identification to the Federal Guard Service personnel.
- Passing through a metal detector and inspection of items brought into the building; note that all items brought to HHS are subject to inspection.

Note: Individuals who are not registered in advance will not be permitted to enter the building and will be unable to attend the meeting in person. The public may not enter the building earlier than 45 minutes prior to the convening of the meeting(s). All visitors must be escorted while in the building.

D. Live Streaming Information

For participants who cannot attend the public meeting in person there will be an option to view the public meeting via live streaming technology. Information on the option to view the meeting via live streaming technology will be posted at a later time on the OHRP Web site at *http://www.hhs.gov/ohrp*. Any other updates to information on the meeting will be posted on the OHRP Web site.

III. Issues for Discussion

HHS invites comment at the public meeting about how an IRB should assess the risks of research involving randomization to one or more standard of care interventions, and what risks of the research should be disclosed to research subjects in the informed consent process. HHS is specifically interested in public input on the following questions:

1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?

a. Under what circumstances should an IRB consider those to be risks that may result from the research?

b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?

c. What type of evidence should an IRB evaluate in identifying these risks?

2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects?

a. What criteria should be used by the IRB to evaluate whether the risks to subjects are reasonably foreseeable?

3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk? Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?

4. How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions? What if the risk significantly varies within the standard of care?

5. Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases the risk of harm, or is it necessary that there be published studies identifying the risk?

IV. Transcripts

As soon as a transcript of the public meeting is available, it will be accessible on the OHRP Web site, *http://www.hhs.gov/ohrp*. A transcript also will be available in either hardcopy or on CD–ROM, after submission of a Freedom of Information request. Written requests are to be sent to the PHS FOIA Office, 7700 Wisconsin Avenue, Suite #920, Bethesda, MD 20857; telephone (301) 492–4800; fax (301) 492–4848; email *FOIARequest@psc.hhs.gov*.

Dated: June 19, 2013.

Howard K. Koh,

Assistant Secretary for Health.

[FR Doc. 2013–15160 Filed 6–25–13; 8:45 am]

BILLING CODE 4150–38–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Meeting of the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health

AGENCY: Office of the Surgeon General of the United States Public Health Service, Office of the Assistant Secretary for Health, Office of the Secretary, Department of Health and Human Services.

ACTION: Notice.

SUMMARY: In accordance with Section 10(a) of the Federal Advisory Committee Act, Public Law 92–463, as amended (5 U.S.C. App.), notice is hereby given that a meeting is scheduled to be held for the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health (the "Advisory Group"). The meeting will be open to the public.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Raju, Tonse (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: RE: SUPPORT FOR PAS
Date: Thursday, June 27, 2013 1:09:09 PM

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no

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Raju, Tonse (NIH/NICHD) [E]
Sent: Thursday, June 27, 2013 12:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: SUPPORT FOR PAS

Hi, did you submit a PAS symposium for the SUPPORT?

Tonse N. K. Raju, MD, DCH
Program Scientist/Medical Officer
Pregnancy and Perinatology Branch
Eunice Kennedy Shriver **National Institute of Child Health and Human Development, 6100 Executive Blvd,**
Bethesda, MD 20892-MS7510
(For FedEx: use Rockville, MD 20852)
phone: 301-402-1872

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Schulke, Hilda (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]
Subject: RE: Dr. Hudson"s availability for the NICHD Neonatal Research Network Steering Committee on July 25-26, 2013
Date: Thursday, June 27, 2013 10:42:06 AM
Attachments: image001.png

Thanks for getting back to me – we will put her on the agenda from **1030-11 am on July 25**. The meeting is at the Neuroscience center, 6001 Executive Blvd, Rockville, MD in room A1/A2. Once we have an updated agenda, I will send it over.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Schulke, Hilda (NIH/OD) [E]
Sent: Thursday, June 27, 2013 10:26 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Jorgenson, Lyric (NIH/OD) [E]
Subject: Dr. Hudson's availability for the NICHD Neonatal Research Network Steering Committee on July 25-26, 2013

Good morning Dr. Higgins:

Per your request below, the best time for Dr. Hudson is Thursday, July 25, 2013 between 10:30 AM and 11:30 AM. Please let us know the exact time you would like her to be there. Also, continue to send us information as it becomes available.

Thank you,

Hilda

NIH National Institutes of Health
Turning Discovery Into Health

HILDA SCHULKE | Staff Assistant
Office of the Dep Director for Science, Outreach, and Policy
NATIONAL INSTITUTES OF HEALTH
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E-mail: Schulkeh@od.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, June 26, 2013 4:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Schulke, Hilda (NIH/OD) [E]
Subject: RE: Request

I would be honored --- let me check my calendar

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, June 26, 2013 4:47 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Request

Hi Kathy,

Thanks for all your help and support for SUPPORT. Our NICHD Neonatal Research Network Steering Committee will meet on July 25-26 at the Neuroscience building (6001 Executive Blvd., Rockville, MD). Alan Guttmacher had planned on attending for a brief 10-15 minute time frame, but is not going to be in town. Many of our investigators have asked about you as you were the first author on the NEJM piece. I know you are extremely busy, but was wondering if you could attend for a short period of time (10-15 minutes)? We are running the meeting from 8 AM – 445 PM on July 25 and 745 AM – 230 PM on July 26. We could accommodate you at any time during the two days. Let me know and thanks again for all your help!

Best regards,

Rose

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From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: OHRP public meeting
Date: Wednesday, June 26, 2013 2:07:21 PM

Rose,
You have my permission to attend.
Marian

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, June 26, 2013 2:04 PM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: OHRP public meeting

Marian
The OHRP public meeting on standard of care/CER research has been posted. The meeting will occur on August 28. I have registered to attend in person. The meeting is downtown at the Humphrey building.

Here is the link--
http://www.hhs.gov/ohrp/newsroom/rfc/Public%20Meeting%20August%2028,%202013/aug28public.html
I would like your approval to attend.
Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "benjamin.wilfond@seattlechildrens.org"; "Davis, Jonathan"
Subject: FW: CTSA CRE Consultation Working Group call on the SUPPORT Study
Date: Wednesday, June 26, 2013 11:25:09 AM
Attachments: CRE KFC consult Workgroup 7 2 13agenda..ppt

Hi
Thank you for inviting me – I will also join the call

Thanks
Rose

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From: CTSA Child Health [mailto:CTSA_ChildHealth@CTSAC4.Org]
Sent: Wednesday, June 26, 2013 10:40 AM
To: CC-CHOC Listserv (list.cc-choc@ctsacentral.org)
Subject: FW: CTSA CRE Consultation Working Group call on the SUPPORT Study

Sent on behalf of Ben Wilfond

Dear CWG member

The next quarterly case discussion for the Clinical Research Ethics (CTSA) Consultation Working Group will be based on the SUPPORT Study on july 2 from 130-100pm ET. Dr. Wally Carlo will kick off the call with a description of the study and the issues that emerged. Our discussion will focus on 4 topics:

- Evaluating risks of standard practice
- Evaluating risks of research
- Evaluating parental permission
- Improving parental permission

This first three will be more conceptual discussions to raise and explore issues, and the final topic will be more action oriented to gauge interest for a CTSA related project?

Attached are some slides with a more detailed agenda.

Because of the broad based interest in this topic, this invitation is being sent to all CRE (ethics) and

CC-CHOC(pediatrics) CTSA members.

Please use GoToTraining as we hope to use the "raise hands" feature to coordinate the discussion.

Click here to register or follow this link https://student.gototraining.com/r/2243373504663308288

Looking forward seeing you in cyberspace.

Benjamin Wilfond MD
Director | Treuman Katz Center for Pediatric Bioethics
Seattle Children's Research Institute
Professor | Department of Pediatrics
University of Washington School of Medicine

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CTSA Clinical & Translational Science Awards

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Lessons from SUPPORT: Improving parental permission in NICU research

July 2, 2013

CRE Consultation Working Quarterly Case Discussion

11:30-1:00 ET

Case Presenter: Wally Carlo MD

University of Alabama

Agenda

- Understanding Support (15 min)
- Discussion
  - Evaluating risks of standard practice (15 min)
  - Evaluating risks of research (15 min)
  - Evaluating parental permission (15 min)
  - Improving parental permission (15 min)

  Wrap up and CRE updates. (15 min)

Understanding SUPPORT

- Describe the state of the science, the rationale for the study, and the views of clinicians about the use of pulse oximetry, when the study was conceived.

- Describe the study design, the primary and secondary end points, and how the level of risk was being imagined by the investigators

- Discuss the consent process used in approaching parents and explaining the study and what worked well and did not.

Evaluating risks of standard practice

- When investigators and clinicians do not agree about the degree of uncertainly about standard care, what are the moral distinctions between providing a standard approach and enrolling infants in a research trial?

Evaluating risks of research

- How should we evaluate the research risks to participants, when comparing standard interventions in a clinical context of high morbidity.

- Should refinements of standard approaches to improve benefits appropriately be considered risks, in the same way that using novel interventions and drugs are?

- Does randomization pose additional risks?

Evaluating Parental Permission

- Is the goal of parental permission to improve understanding and promote decision-making for research participation?

- Do we know what is the best way to get permission from parents for research for prematurely born infants, which is often emergent and stressful?

Improving Parental Permission

- How do we improve written materials and what other interventions might help?

- What role can CTSAs play to improving the approach to parental permission?

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
Date: Tuesday, June 25, 2013 1:31:00 PM
Attachments: 322943 - Control Sheet.pdf
322943 - Incoming - 1 Support Study and NIH Censorship of Dissenting Opinions.pdf
322943 - Incoming - Ia 130613 Letter to HHS Secretary.pdf
Importance: High

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From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Thursday, June 20, 2013 2:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
Importance: High

Hi – I believe Rose is out this week? We just received this control (as Sandy pointed out, previously it was just sent to us FYI, but now they want us to draft the response for the Secretary). It's due next Thursday to Building 1, but Alan would like to see the response before it goes over.

I don't have any of the facts about Dr. Natanson, so I can't even start a draft. Can you help draft, or steer me in the right direction, please?

Sorry!

Lisa

Lisa Kaeser, J.D.
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From: Ott, Sandra (NIH/NICHD) [E]
Sent: Thursday, June 20, 2013 2:11 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
Importance: High

Lisa,

This originally came in as an FYI on June 13. Today this was assigned to NICHD to prepare a draft for the Secretary's Signature and is due by June 27. We are to prepare a draft response for the Secretary's signature and a Summary Statement. We are to return to ES in DDRMS by COB June 27. The PA on this is Michelle Whitfield.

Sandy.

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
Sent: Thursday, June 20, 2013 12:59 PM
To: Brown, Crystal (NIH/NICHD) [C]; Ott, Sandra (NIH/NICHD) [E]; Wood, Vandora (NIH/CIT) [C]
Subject: WF 322943 - Create and Assemble Response (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

You have received a task notification requiring your attention.

Additional instructions are included on the task form, please click the following link to open the task:

Task

Please do not reply to this email, this is an automated message.

If you have concerns please contact the NIH Help Desk at (301) 496-4357.

Work Folder Information
Work Folder: WF 322943
Process: IC Response CreationWF 322943
Due Date: June 27, 2013
Program Analyst: Whitfield, Michelle D. (NIH/OD) [E]
WF Subject: Letter from Public Citizen's Health Research Group complaining about NIH expert that was silenced because he previously raised concerns about the SUPPORT study
IC:NICHD
From: Carome, Michael;
To: Sebelius, Kathleen;Collins, Francis;

Remarks: Assigned to NICHD for response creation to prepare a draft Sec Sig by June 27. Please prepare a draft response for the Secretary's signature and a Summary Statement and return to ES by c.o.b. June 27. Thank you.

Secretary's Correspondence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

OS#:	**061820131033**	*Date on Letter:*	**6/13/2013**
From:	**Carome, Michael (Public Citizen's Health Research Group)** **Wolfe, Sidney M. ()**		
City/State:	**Washington DC**	*Date Received:*	**6/18/2013**
On Behalf Of:	**,**	*Type:*	**Major Organization**
Subject:	**Censorship of an Expert Within the National Institutes of Health Who Holds Views Contrary to Those of NIH Leadership Regarding the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT study)**		
Synopsis:			
Subject Tags:	**None**		

Assigned to:	**NIH**		
PC:	**Jamar Hawkins**	*Date Assigned:*	**6/20/2013**
Action Required:	**Sec Sig**	*Date Reassigned:*	
		Reply Due Date:	**7/4/2013**

Info Copies To:	**ASPE; OASH; OGC; Oliver Potts; IEA; ESS; Jamar Hawkins**		
Interim (Y/N):	**No**	*Date Interim Sent:*	
Comments:			
File Index:	**PO-4-12**	*CCC:*	**Elaine Gross**

From: Michael Carome
Sent:13 Jun 2013 07:16:45 -0400
To: Sebelius, Kathleen (HHS/OS)
Cc: Collins, Francis (NIH/OD) [E];Guttmacher, Alan (NIH/NICHD) [E]
Subject: The SUPPORT study and NIH Censorship of Dissenting Opinions
Attachments:130613_Letter to HHS Secretary Re Censorship of Dissenting Opinions on SUPPORT_FINAL.pdf

Dear Secretary Sebelius:

Attached please find a letter from Public Citizen□s Health Research Group regarding additional concerns about the NIH-funded SUPPORT study involving extremely premature infants. The original hardcopy of our letter will follow by regular mail.

Thank you for your attention to this important matter.

Sincerely,

Michael A. Carome, M.D.

Director, Health Research Group

Public Citizen

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June 13, 2013

The Honorable Kathleen Sebelius
Secretary
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

RE: Censorship of an Expert Within the National Institutes of Health Who Holds Views Contrary to Those of NIH Leadership Regarding the Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is deeply troubled to learn that the National Institutes of Health (NIH) has silenced an expert within the agency who has previously raised serious concerns about the ethics of clinical trials with designs that are very similar, if not identical, to that of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT study) involving extremely premature babies.

Dr. Charles Natanson, Senior Investigator and Chief of the Anesthesia Section in the NIH Clinical Center's Critical Care Medicine Department, was invited by Bloomberg BNA to co-present a continuing legal educational (CLE) webinar in July regarding the SUPPORT study. Also invited to participate in the webinar are Dr. Michael Carome, Director of Public Citizen's Health Research Group, and Dr. Arthur L. Caplan, a bioethicist at the New York University Langone Medical Center.

Dr. Natanson is one of the world's leading experts on how to safely design clinical trials testing titrated therapies in critically ill patients where death is one of the primary endpoints, as was the case with the SUPPORT study. He is one of the most published authors on this topic[1,2,3,4,5,6] and

[1] Deans KJ, Minneci PC, Eichacker PQ, Natanson C. Defining the standard of care in randomized controlled trials of titrated therapies. *Curr Opin Crit Care.* 2004;10(6):579-82.
[2] Deans KJ, Minneci PC, Suffredini AF, et al. Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols. *Crit Care Med.* 2007;35(6):1509-1516.
[3] Minneci PC, Eichacker PQ, Danner RL, et al. The importance of usual care control groups for safety monitoring and validity during critical care research. *Intensive Care Med.* 2008;34(5):942-947.
[4] Deans KH, Minneci PC, Klein HG, Natanson C. The relevance of practice misalignments to trials in transfusion medicine. *Vox Sang.* 2010;99(1):16-23.
[5] Deans KJ, Minneci PC, Danner RL, et al. Practice misalignments in randomized controlled trials: identification, impact, and potential solutions. *Anesth Analg.* 2010;111(2):444-450.
[6] Deans KJ, Minneci P, Eichacker PQ, et al. Walk a mile in whose shoes? *Anesth Analg.* 2010;111(2):576-577.

has spoken about it at numerous conferences around the world. NIH is very familiar with his expertise in this regard. Dr. Natanson recently spoke publicly at international conferences about design problems related to the SUPPORT study and other similar studies that raise serious ethical concerns with respect to the protection of human subjects.

Bloomberg BNA recently asked NIH to allow Dr. Natanson to participate in the July CLE webinar on the SUPPORT study, and NIH denied the request. This denial was communicated to Bloomberg BNA by NIH Public Affairs Specialist Renate Myles, who stated that "we are declining participation in the webinar at this time due to a forthcoming public meeting announced by [the Department of Health and Human Services] HHS: http://www.hhs.gov/ohrp/ on IRB process for trials randomizing participants within the standard of care."

We are dismayed by the hypocrisy that NIH has sought to gag a renowned expert such as Dr. Natanson, who has identified serious concerns about the ethics of the study design used in the SUPPORT study, while at the same time allowing other NIH officials the freedom to speak publicly about the study as long as their positions are favorable to the NIH party line. Indeed, just last week, with full knowledge of the same forthcoming public meeting referenced above, the NIH Director and two senior colleagues, including the director of the NIH institute that funded the SUPPORT study, published a commentary article on the topic in the *New England Journal of Medicine*. This article defended the ethics, design, and consent procedures of the SUPPORT study and contested the findings by the Office for Human Research Protections that the study's consent forms failed to disclose the risks of the research, including the possible increased risk of death, to the parents of the subjects.[7]

This concerted effort by NIH officials to publicly promote a one-sided, biased defense of the study and to suppress an alternative viewpoint voiced by a well-informed NIH expert ultimately undermines the mission and integrity of the agency. As one of the premier academic institutions in the world, NIH should welcome and encourage the full and free expression of diverse ideas rather than engage in unacceptable censorship of its own physician scientists.

The fact that HHS plans to convene a public meeting to discuss issues related to the SUPPORT study is a flimsy excuse for preventing an expert such as Dr. Natanson from discussing that study in a public academic forum.

We encourage you to immediately investigate NIH's policies regarding participation of agency scientists in legitimate public forums and direct NIH to stop censoring experts who have well-reasoned, evidence-based critiques of the SUPPORT study or any other NIH-funded research.

[7] Hudson KL, Guttmacher AE, Collins FS. In support of SUPPORT — A view from the NIH. *N Engl J Med.* Published online June 5, 2013. DOI: 10.1056/NEJMp1306986.

Thank you for your attention to this important matter.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Senior Advisor and Founder
Public Citizen's Health Research Group

cc: Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development

From: Stevens, Timothy
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: revised manuscript
Date: Monday, June 24, 2013 10:05:43 PM
Attachments: Manuscript - 6-15-13.docx
Manuscript - Tables and Figures - 6-5-13 columns.docx
Reply to Reviewers.docx

Hi Rose and Stephanie,

Attached is the revised manuscript including tables and figures as well as my reply to the editor and reviewers. Can you please forward to the coauthors?

A couple things:

- In the document entitled reply to reviewers, I copied the text from the Pediatrics Decision letter, bolded the editor and reviewer comments and wrote my reply in red font. I hope this will make reviewing my replies easier.
- Below I copied the two comments made by the editor (bold) along with my replies (italics).

1. **"It appears that not all the coauthors listed meet the authorship criteria."**

   Stephanie – can you update the author list and their roles? If there is an appropriate way to shorten the author list, it may help us. We will need to make this as strong as possible.

2. **"Please address the ethical concerns about the original study."**

   In a letter dated June 4th, 2013, Lisa Buchanan, Compliance Officer for the Department of Health and Human Service's Office of Human Research Protection (OHRP), stated that "OHRP does not and never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent." In addition, she writes, "we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic. In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further action in studies involving similar designs until the process of producing appropriate guidance is completed." (http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf).

   Based upon these comments, the following sentences have been added to the revised manuscript, "The SUPPORT Study and its design were deemed ethical by the Department of Health and Human Service's Office of Human Research Protection

(OHRP). OHRP has initiated a public discussion of the adequacy of the written informed consent used in SUPPORT and similar trials of clinical practices that are within the range of standard of care at the time the research study was performed."

I'd like to have all replies by July 4th if possible.

Thanks for your help

Tim

Respiratory Outcomes of the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT)

Timothy P. Stevens, MD MPH[1]; Neil N. Finer, MD[2]; Waldemar A. Carlo, MD[3]; Peter G. Szilagyi, MD[1]; Dale L. Phelps, MD[1]; Michele C. Walsh, MD MS[4]; Marie G. Gantz, PhD[5]; Abbot R. Laptook, MD[6]; Bradley A. Yoder, MD[7]; Roger G. Faix, MD[7]; Jamie E. Newman, PhD, MPH[5]; Abhik Das, PhD[8]; Barbara T. Do, MSPH[5]; Kurt Schibler, MD[9]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Richard A. Ehrenkranz, MD[10]; Myriam Peralta-Carcelen, MD MPH[3]; Betty R. Vohr, MD[6]; Deanne E. Wilson-Costello, MD[4]; Kimberly Yolton, PhD[9]; Roy J. Heyne, MD[11]; Patricia W. Evans, MD[12]; Yvonne E. Vaucher, MD MPH[2]; Ira Adams-Chapman, MD[13]; Elisabeth C. McGowan, MD[14]; Anna Bodnar, MD[7]; Athina Pappas, MD[15]; Susan R. Hintz, MD MS Epi[16]; Michael J. Acarregui, MD[17]; Janell Fuller, MD[18]; Ricki F. Goldstein, MD[19]; Charles R. Bauer, MD[20]; T. Michael O'Shea, MD MPH[21]; Rosemary D. Higgins, MD[22] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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[5] Social, Statistical & Environmental Sciences, RTI International, Research Triangle Park, NC
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[8] Social, Statistical & Environmental Sciences, RTI International, Rockville, MD
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[12] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
[13] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
[14] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA
[15] Department of Pediatrics, Wayne State University, Detroit, MI
[16] Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA
[17] Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)
[18] University of New Mexico Health Sciences Center, Albuquerque, NM
[19] Department of Pediatrics, Duke University, Durham, NC
[20] University of Miami Miller School of Medicine, Miami, FL
[21] Wake Forest University School of Medicine, Winston-Salem, NC
[22] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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Short Title: Respiratory Outcomes of the CPAP and Oximetry Trial

Abbreviations:
BPD – Bronchopulmonary Dysplasia
CA - Corrected Age
CPAP – Continuous Positive Airway Pressure
NICHD - National Institute of Child Health and Human Development
NRN – NICHD Neonatal Research Network
ROP – Retinopathy of Prematurity
SUPPORT - Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

Key Words: Text: MeSH terms:
Bronchopulmonary Dysplasia
Infant, Newborn
Infant, Low Birth Weight
Infant, Extremely Low Birth Weight
Infant, Premature
Infant, Extremely Low Gestational Age
Infant mortality
Respiratory morbidity
Intensive care, neonatal
Hospital Readmission
Oximetry
Randomized controlled trial
Retinopathy of prematurity (ROP)
Continuous Positive Airway Pressure
Intubation, endotracheal
Pulmonary surfactants/therapeutic use
Oxygen inhalation therapy/methods
Oxygen administration & dosage
Follow-up studies

Funding Sources: The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2004-2009; Follow-up 2006-2011). In addition to the grants listed in the acknowledgements section below, NICHD also provided grant support for the SUPPORT Breathing Outcomes Secondary Protocol to Dr. Stevens (K23 HD50646)

Financial Disclosure Statement: The authors gratefully recognize the generous support of NICHD and NHLBI as identified in the acknowledgements section below. The authors have no other financial relationships relevant to this article to disclose.

Conflict of Interest Statements: The authors have no conflicts of interest to disclose.

Clinical Trial Registry Name: Surfactant Positive Airway Pressure and Pulse Oximetry Trial (Support); ClinicalTrials.gov number, NCT00233324.

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ABSTRACT

BACKGROUND:
The NICHD SUPPORT Trial, using a factorial design that randomized extremely preterm infants to high versus low oxygen saturation targets and delivery room (early) CPAP or intubation, found no significant differences in the primary composite outcome of death or BPD. We wished to explore long term pulmonary outcomes of these infants.

METHODS:
The Breathing Outcomes Study assessed respiratory morbidity among infants enrolled in SUPPORT at 6 month intervals from hospital discharge to 18-22 months corrected age (CA). Two pre-specified primary outcomes, wheezing more than twice per week during the worst 2 week period and cough lasting more than 3 days without a cold were compared between each randomized intervention.

RESULTS:
One or more interviews were completed for 918 of 922 (99.6%) eligible infants. The incidence of wheezing and cough were 47.9% and 31.0%, respectively, and did not differ between study arms of either randomized intervention. Among secondary outcomes, infants randomized to low versus high oxygen saturation targets had a lower incidence of wheezing (36.3% vs. 43.4%, $p<0.05$). Infants randomized to CPAP versus intubation had fewer episodes of wheezing without a cold (28.9% vs. 36.5%, $p<0.05$), respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%, $p<0.05$) and physician or emergency room visits for breathing problems (68.0% vs. 72.9%, $p<0.05$) at 18-22 months CA.

CONCLUSION:
Low rather than high oxygen saturation targets may be associated with less wheezing by 18-22 months CA. Early CPAP rather than intubation and surfactant results in less respiratory morbidity by 18-22 months CA.

Abstract Word Count: 247

BACKGROUND

Extremely preterm infants are at greater risk of respiratory morbidity and need for pulmonary care in early childhood than later preterm or term infants [1-7] and contribute substantially to the public health burden of childhood respiratory disease in the United States.[8] Lung injury, which may result from mechanical ventilation and supplemental oxygen exposure in the early neonatal period, has been identified as risk factors for development of Bronchopulmonary Dysplasia (BPD) and pulmonary morbidity in infancy, childhood and beyond.[1,2,9,10] Though infants with BPD are at highest risk for poor pulmonary outcome, neonates without BPD are also at risk for airway dysfunction and pulmonary morbidity during infancy.[4,11]

The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) conducted by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) studied infants 24 0/7th - 27 6/7th weeks' gestation treated with each of two respiratory strategies designed to minimize mechanical ventilation and supplemental oxygen exposure: 1) lower (85-89%) compared with higher (91-95%) oxygen saturation targets and 2) early non-invasive continuous positive airway pressure (CPAP) compared with early intubation and early surfactant administration (Surfactant). Our Network previously reported results of SUPPORT demonstrating no significant differences in the composite outcomes of death or BPD and death or neurodevelopmental impairment between infants randomized to either of the two respiratory interventions.[12-14] It is important to note that although the composite incidence of death or BPD was similar, infants randomized to lower rather than higher oxygen saturation targets had significantly lower incidences of retinopathy of prematurity but significantly greater mortality.

We now report on The Breathing Outcomes Study, a sub study to the SUPPORT Trial, which compared respiratory morbidities among extremely preterm infants treated with the SUPPORT study interventions as neonates. It was hypothesized that infants randomized to lower rather than higher oxygen saturation targets and CPAP rather than early intubation and surfactant will each have less frequent episodes of wheezing and cough and, as a secondary outcome, less need for outpatient pulmonary care at 18-22 months' corrected age (CA).

METHODS

Infants eligible for The Breathing Outcomes Study were infants enrolled in SUPPORT who survived to hospital discharge and consented for enrollment into the study. One thousand three hundred sixteen (1316) infants from 20 centers across the United States were enrolled into SUPPORT between February 2005 and February 2009 and seen in follow-up between 2006 and 2011. As a sub study to SUPPORT, Breathing Outcomes gained approval and began recruitment after SUPPORT began enrollment. As a result not all SUPPORT patients were successfully recruited into Breathing Outcomes. Written informed consent to participate in Breathing Outcomes was obtained either at the time of enrollment into SUPPORT or separately for those patients already enrolled in SUPPORT. The study was approved by the institutional review boards at all participating Network centers and by RTI International, the data center for the NICHD Neonatal Research Network. Data collected at participating sites were transmitted to RTI International, which stored, managed, and analyzed the data for both SUPPORT and Breathing Outcomes.[12,13] The SUPPORT Study and its design were deemed ethical by the Department of Health and Human Service's Office of Human Research Protection (OHRP). OHRP has initiated a public discussion of the adequacy of the written informed consent used in

SUPPORT and similar trials of clinical practices that are within the range of standard of care at the time the research study was performed.[15]

Interventions of the SUPPORT Trial

Subjects enrolled in SUPPORT were randomly assigned prior to delivery to receive CPAP after birth, followed by a limited ventilation strategy if intubation were needed or to intubation in the delivery room and receipt of prophylactic surfactant by 1 hour of age. Using a 2x2 factorial design, SUPPORT subjects were also randomly assigned to treatment with either an oxygen saturation target of 85% to 89% (lower saturation group) or with a target of 91% to 95% (higher saturation group). Research methods for study enrollment, intervention, data collection and primary analyses have been previously reported.[13] The primary outcome of SUPPORT was the incidence of death or physiologic BPD which was defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen. Traditional BPD was defined by the receipt of any supplemental oxygen at 36 weeks.[16]

Assessments of the Breathing Outcomes Study

For subjects enrolled in Breathing Outcomes, a parent or primary caregiver was interviewed by research staff either in person or by phone using structured questionnaires and interview scripts at each of 4 time points; at or near the time of hospital discharge and at or near 6, 12 and 18-22 months CA. The study questionnaires were drafted based upon questionnaires developed, validated and used with permission of the Tucson Children's Respiratory Study.[17,18] Questions were added to the Tucson questionnaires to more fully elicit the frequency and characteristics of

respiratory signs, including wheezing and cough; incidence of physician-diagnosed asthma, reactive airway disease or BPD exacerbation or flare-up; incidence of bronchiolitis, bronchitis or pneumonia, croup; use of medications to treat respiratory illnesses including diuretics, nebulized bronchodilators, inhaled steroids, systemic steroids or oxygen; use of health services including respiratory related physician visits, emergency room visits and hospitalizations; use of preventive therapies including palivizumab and influenza immunization; and impact on the family including whether the parent or caregiver needed to change plans due their child's breathing.

To standardize administration of the interview, a lead interviewer at each participating center underwent training consisting of a teleconference with 1 of 2 project trainers (Rochester site) to discuss each study question and the written interview script associated with it. Interview trainees then interviewed a standardized patient simulated by the project trainers. Lead interviewers at each center were then able to train additional interviewers at their sites as needed. To minimize misinterpretation of other respiratory sounds as wheezing, a verbal description of wheezing and a brief audio clip of wheezing were played for the interviewee at the beginning of the interview. Questionnaires originally written in English were translated into Spanish using a certified translation service (Cornell Translation Service, Ithaca, NY). Interviews were conducted in either English or Spanish as appropriate.

To minimize loss of recall over time, the four interviews were conducted at approximately 6 month intervals beginning at the time of hospital discharge.[19] Study personnel conducted the first parent interview using a questionnaire designed to collect information on family history of respiratory diseases and atopy, home environment including tobacco and pet exposures, and diet at discharge from the hospital. Based upon the preference of each participating center, the 6, 12 and 18-22 month interviews were conducted either by trained staff at the local center (15 centers)

or by long distance telephone interview from the Rochester center (5 centers). At each of the 6, 12 and 18-22 month interviews, the parent or caregiver was asked to base their responses on the 6 month interval since the last interview. If an interview at one time point was not completed, parents were asked to base their responses during the next interview upon the interval history since the last completed interview. Taken together, the four questionnaire series administered by interviewing the parent or primary caregiver was designed to provide a complete respiratory history over the first 18-22 months' CA. In addition to reporting interview responses during the first 18-22 months CA (defined as the combined responses to the 6, 12, 18-22 month interviews and listed as 18-22 months in table 3), we report responses from the 6 month interview because preterm infants are at especially high risk of respiratory morbidity during the first 6 months of age.[20]

Outcomes

Primary Outcomes: Two primary outcomes were assessed by parental report: the incidence of wheezing more than twice per week and incidence of cough lasting more than 3 days without a cold. The incidence of wheezing was ascertained using the primary question used and validated in the Tucson Study (a large prospective birth cohort study of term infants), "Has his/her chest sounded wheezy or whistling?". [17] The outcome for wheezing more than twice per week was considered positive if the parent selected "More than two times a week" in response to the question, "during the worst 2 week period, how often has your child's chest sounded wheezy or whistling". The incidence of cough lasting more than 3 days was ascertained using the Tucson question, "Has your child had a cough for 3 days or more when he/she did not have a cold?".[17]

Secondary outcomes and covariates: Secondary outcomes were interview responses to the 6, 12 and 18-22 month questionnaires for respiratory signs, physician diagnosed respiratory diseases, medication use, health services use and impact on the family. In addition, the incidence of the combined outcome, wheezing more than twice per week or cough lasting more than 3 days, was also assessed. To assure that follow up cohorts were comparable, the following covariates were evaluated: intake of at least some breast milk; family history of inhaled or food allergies, asthma, COPD or emphysema, or other chronic respiratory illness; environmental exposures tobacco smoke, daycare, children under 12 years old and pets; and use of preventive therapies as outlined above. In addition, each patient's outcomes from SUPPORT were available to the Breathing Outcomes Study analysis.

Statistical Analyses

For Breathing Outcomes, a sample size of 817 subjects was calculated as necessary to detect an absolute risk difference of 0.1 in the incidence of the primary outcome of wheezing more than twice per week between groups with 90% power and alpha of 0.05 assuming an 80% minimum follow-up rate and baseline incidence of wheezing more than twice per week of 29%.[21] Sample size calculations for SUPPORT have been reported. [12,13] Based upon SUPPORT's target enrollment of 1310 patients and assuming a 22% mortality (NICHD historical data for calendar year 2000), we anticipated 1021 patients potentially eligible for the Breathing Outcomes Study.

Responses were tabulated by using the number of subjects with a positive response at a given time point or time interval as the numerator and the number of subjects completing a survey at that time point as the denominator (893 and 918 completed surveys for the 6 and 18-22 month time points, respectively). Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables. For

categorical variables with low frequency (n<5), Fisher exact tests were used. The two primary analyses used the number of patients with either wheezing more than twice per week or cough lasting more than 3 days as the numerator and the number of infants for whom that outcome was known as the denominator. Using Poisson regression models to adjust for gestational age stratum, study center and familial clustering, adjusted relative risk (ARR) values and 95% confidence intervals were calculated and are reported. When Poisson models did not converge, relative risk adjusted for gestational age and center is reported (indicated in tables by †). When the two adjustment models failed to converge due to low prevalence (<5%), unadjusted relative risks are reported (indicated by †† in table). Results were considered statistically significant if the two-sided p value was less than 0.05; a trend towards significance was considered if the two sided p value was between 0.05 and 0.10 inclusive. Because testing did not identify significant interaction effects between groups, only marginal (main) effects are reported. No adjustments have been made for multiple comparisons. All calculations were performed using SAS software (Cary, NC).

RESULTS

Of the 1316 patients enrolled in SUPPORT, 922 were eligible and gave consent to participate in the Breathing Outcomes Study. The 918 subjects with at least one completed questionnaire were considered the study cohort (Figure 1). Follow up rates at each time point are listed in Figure 1. Parents of 873 infants completed the four questionnaire series (94.7%).

Characteristics of the follow-up cohort

Among the follow up cohort, the group randomized to lower compared with higher oxygen saturation targets had fewer non-Hispanic white patients and a lower proportion of patients with

BPD defined using the traditional criteria of supplemental oxygen use at 36 weeks' post menstrual age (PMA). The group randomized to CPAP and limited ventilation had similar demographics and neonatal outcomes as the group randomized to Surfactant (Table 1). There was no significant difference between groups in the proportion of infants with BPD defined using the physiologic definition. Family history and environmental exposure histories were similar between the lower and higher oxygen saturation target groups and the CPAP and Surfactant groups (Table 2).

Overall in the Breathing Outcomes cohort during the first 18-22 months CA, wheezing more than twice per week was reported in 47.9% of patients, cough lasting more than 3 days in 31.0% and either wheezing more than twice per week or cough more than 3 days in 68.2%. Among cohort subjects, use of inhaled (26.3%) and/or systemic steroids (9.4%) was common. Cohort subjects also had high use of physician visits (63.8%), emergency room visits (46.6%) and hospitalizations for wheezing or breathing problems (31.0%).

Primary Outcomes

There was no difference in incidence of the two primary outcomes, wheezing more than twice per week and cough lasting more than 3 days, between infants randomized to lower compared with higher oxygen saturation targets nor between infants randomized to treatment with CPAP rather than Surfactant (Table 3). The combined outcome of episodes of wheezing more than twice per week or cough lasting more than 3 days for the overall cohort was 64.6% and did not differ significantly between infants randomized to lower rather than higher oxygen saturation target or CPAP rather than Surfactant (Table 3).

Secondary Outcomes

Oxygen Saturation Targeting Intervention

At 6 months CA, infants randomized to lower compared with higher oxygen saturation targets had a lower incidence of wheezing and in use of nebulized medications since NICU discharge (36.3% vs. 43.4%, $p< 0.05$ and 1.2% vs. 3.9%, $p= 0.02$, respectively) (Table 3). Supporting these differences in wheezing was a trend toward a lower incidence of wheezing more than twice per week during the patient's worst 2 week period (22.0% vs. 27.7%, $p=0.06$) (Table 3). Over the first 18-22 months CA, infants treated with lower rather than higher oxygen saturation targets were less likely to have episodes of wheezing without a cold (28.4% vs. 36.3%, $p=0.01$) (Table 3).

Early CPAP Intervention

At 6 months CA, infants randomized to treatment with CPAP rather than Surfactant were reported to have fewer asthma, reactive airway disease or BPD exacerbation or flare-up episodes diagnosed by a doctor since NICU discharge (12.3% vs. 17.2%, $p< 0.05$) and a trend toward fewer hospitalizations for wheezing or breathing problems (16.5% vs. 27.0%, $p=0.09$). Perhaps related to these differences, parents or primary caregivers of infants randomized to CPAP were less likely at 6 months CA to report changing their plans due to their child's breathing problems (12.8% vs. 20.4%, $p<0.01$)(Table 3).

During the first 18-22 months CA, infants randomized to early CPAP versus Surfactant were significantly less likely to have wheezing episodes occurring without a cold (28.9% vs. 36.5%, $p=0.01$), respiratory illnesses diagnosed by a doctor (one or more episodes of asthma, reactive airway disease or BPD exacerbation or flare up or bronchiolitis, bronchitis or pneumonia) (47.7% vs. 55.2%, $p=0.02$), wheezing or breathing problems that prompted a physician or

emergency room visit (68.0% vs. 72.9%, $p<0.05$). Compared with those of infants in the Surfactant group, parents or guardians of infants in the CPAP group were also less likely to report changing their plans due to their child's breathing problems (32.4% vs. 39.0%, $p<0.05$).

DISCUSSION

We report results of the Breathing Outcomes Study, a sub study to SUPPORT, which sought to quantify respiratory morbidity by 18-22 months corrected age for extremely premature children born 24-27 weeks gestation. We found no significant differences at 18-22 months CA in the incidence of either of the two primary outcomes, wheezing more than twice per week or cough lasting more than 3 days without a cold, between patients randomized to lower versus higher oxygen saturation targets or randomized to CPAP versus intubation and early Surfactant.

In secondary analyses, extremely preterm infants randomized to low compared with high oxygen saturation targets were less likely to have wheezing or use a home nebulizer at 6 months CA and to have wheezing apart from a cold between discharge and 18-22 months CA. Several pulmonary outcome studies have found an association between neonatal oxygen exposure and expiratory flow dysfunction and airway hyperreactivity among infants with or without BPD. [2,7,22-24] Though patients treated with lower compared with higher saturation targets in SUPPORT had a shorter duration of oxygen exposure, they had greater mortality, similar incidence of BPD, and based results of the Breathing Outcomes Study, similar use of outpatient services for respiratory care and only minor differences in the incidence of respiratory signs. Based on these findings, if oxygen related pulmonary morbidity is to be minimized, strategies of reducing oxygen exposure and oxidant injury other than targeting lower oxygen saturations will be needed. [21,25]

Patients randomized to CPAP and limited ventilation rather than intubation and surfactant administration within 1 hour had fewer asthma, reactive airway disease or BPD exacerbation or flare-up episodes at 6 months CA and a trend toward fewer hospitalizations for respiratory problems. Perhaps related to these findings was a significant reduction in the proportion of parents reporting that they needed to change plans due to their child's breathing difficulties. During the first 18-22 months CA, patients randomized to early CPAP rather than Surfactant were significantly less likely to have had wheezing episodes occurring without a cold, respiratory illnesses diagnosed by a physician or physician or emergency room visits for breathing or wheezing problems. Parents of CPAP compared with Surfactant group infants were less likely to report changing their plans due to the child's breathing problems. These respiratory benefits were found in spite of the fact that the proportion of children with BPD, defined using either the traditional or physiologic criteria[16], was similar between CPAP and Surfactant arms in the SUPPORT study and in the Breathing Outcomes' follow-up cohort. Our data are consistent with follow up data from The COIN Trial, which despite finding no difference in the incidence of death or BPD among 610 infants randomized to either CPAP or conventional management, found better pulmonary function at 8 weeks corrected among a 39 patient subcohort of study infants randomized to CPAP. [26,27] These observations suggest that treatment of infants 24-27 6/7 weeks gestation at risk for RDS with CPAP is associated with respiratory benefits that are unapparent or underestimated by the incidence of BPD alone and that longitudinal assessment of pulmonary morbidity is necessary to fully evaluate the potential benefits of respiratory interventions in randomized clinical trials.

We found that regardless of treatment arm, respiratory signs and use of health care are common among infants 24-27 6/7th weeks' gestation during the first 18-22 months CA. Over two-thirds of

subjects in the Breathing Outcomes Study cohort reported wheezing more than twice per week or a cough lasting more than 3 days. Treatment of these respiratory signs was not only associated with frequent use of both inhaled and systemic steroids, medications that have potential long term effects on growth and development, [28,29] but also with frequent physician and emergency room visits and hospitalizations, health services which contribute greatly to health care costs.[8]

The strengths of this study include the large number of extremely preterm infants enrolled. This is the largest respiratory follow up study of a randomized clinical trial. Other strengths include the high follow up rates for enrolled patients and use of comprehensive respiratory questionnaires administered in a scripted interview by trained personnel. Though not as objective as pulmonary function testing, respiratory history was used as outcome measures due to clinical and financial concerns associated with use of invasive pulmonary testing and potential complications of sedation in former preterm infants. In addition, parental report of wheezing has been shown to correlate with pulmonary function testing and data extracted from office records and provides an estimate of the burden of respiratory morbidity to the patient and family as well as the health care system. [19,30] Among potential weaknesses, respiratory history data were taken by parental report, which has the potential for classification and recall bias. To minimize classification bias, all primary and follow up study data of this randomized trial were collected in a blinded manner. Hence, though it may affect the precision of point estimates, classification bias is unlikely to have introduced systematic bias into our study that favors one study arm over another. To reduce recall bias, parent interviews were conducted at 6 month intervals.[19] Because the Breathing Outcomes Study was approved and began enrollment after SUPPORT had begun and because we wished to follow all available SUPPORT subjects, study results are not reported as competing outcomes (e.g. death or wheezing more than twice per week) but rather as

respiratory outcomes of the cohort of SUPPORT subjects that survived to hospital discharge. As has been previously reported, the results of SUPPORT and thereby potentially the follow up studies associated with it may not be fully generalizable to all extremely preterm infants because the need for antenatal consent resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort. [31]

In summary, we found no significant differences in the incidence of wheezing more than twice per week or cough lasting more than 3 days at 18-22 months CA between extremely preterm survivors who were randomized at delivery to either lower versus higher oxygen saturation targets or early CPAP versus Surfactant. In secondary analyses, we found minor reductions in the incidence of wheezing and nebulizer use at 6 months and wheezing without a cold at 18-22 months CA in the lower oxygen saturation group. Also in secondary analyses, we report fewer respiratory signs, physician diagnosed respiratory problems and reduced health care use to treat respiratory problems among infants randomized to CPAP rather than early surfactant administration. Results of SUPPORT and neurodevelopmental follow up of SUPPORT patients found no deleterious effects of CPAP over Surfactant.[12-14] Those findings coupled with the respiratory outcomes reported here suggest that treatment of extremely premature infants with CPAP and limited ventilation rather than intubation and early Surfactant administration is safe and may result in less respiratory morbidity during the first 18-22 months CA. Lastly, our findings demonstrate a high risk of post-discharge respiratory morbidities among preterm infants 24-27 6/7 weeks gestation that not only require close medical monitoring but also pose potential burdens to families as well as to society by increasing health care costs.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial (Recruitment 2004-2009; Follow-up 2006-2011). In addition to the grants listed below, NICHD also provided grant support for the SUPPORT Breathing Outcomes Secondary Protocol to Dr. Stevens (K23 HD50646).

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We wish to acknowledge the Tucson Children's Respiratory Study (Marilyn Lindell, RN), Tucson, AZ for support of this project by sharing respiratory symptom questionnaires which were adapted for use in this study.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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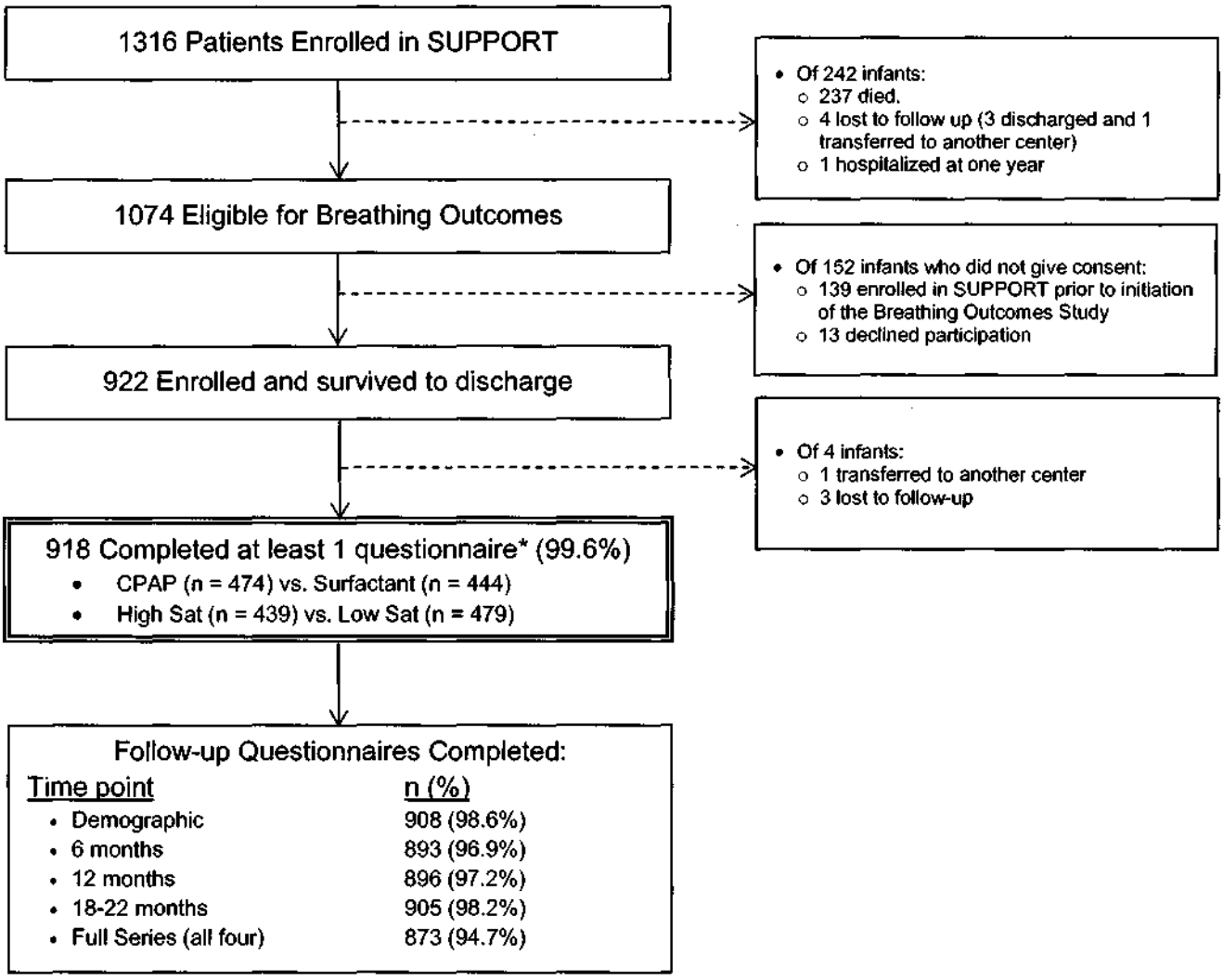
Figure 1. Consort diagram including follow up rates.



* Follow-up Cohort

Table 1.

Demographic and neonatal characteristics of follow-up cohorts.

	Low Sat N=439	High Sat N=479	CPAP N=474	Surfactant N=444
Birth Weight (g, mean ± s.d.)	858 ± 186	844 ± 190	850 ± 184	851 ± 193
Gestational Age (w, mean ± s.d.)	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0
24 wks 0 days - 25 wks 6 dys - no. (%)	158 (35.5)	184 (37.5)	183 (37.7)	159 (35.3)
25 wks 0 days - 27 wks 6 dys - no. (%)	287 (64.5)	307 (62.5)	303 (62.4)	291 (64.7)
Male - no. (%)	222 (49.7)	264 (53.8)	238 (49.0)	248 (54.9)
Non-Hispanic Black - no. (%)	168 (37.6)	157 (32.0)	173 (35.6)	152 (33.6)
Non-Hispanic White - no. (%)	176 (39.4) *	226 (46.0)	196 (40.3)	206 (45.6)
Hispanic - no. (%)	88 (19.7)	91 (18.5)	98 (20.2)	81 (17.9)
Other/unknown - no. (%)	15 (3.4)	17 (3.5)	19 (3.9)	13 (2.9)
Length of NICU Hospitalization (median (min-max))	90 (39 - 365)	93 (46 - 366)	91 (44 - 366)	93 (39 - 365)
BPD (supplemental O2) - no. (%)	160 (36.3) **	221 (45.8)	187 (39.1)	194 (43.5)
BPD (physiologic definition) - no. (%)	165 (37.4)	193 (40.0)	183 (38.3)	175 (39.2)
Discharged home on oxygen - no. (%)	105 (24.0)	111 (23.2)	108 (22.8)	108 (24.4)
Discharged home on respiratory medications - no. (%)	101 (27.3)	106 (27.1)	110 (27.8)	97 (26.6)
Discharged home October - March - no. (%)	232 (52.9)	227 (47.5)	232 (48.8)	227 (51.4)

* Low sat vs. high sat, $p < 0.05$
** Low sat vs. high sat, $p < 0.01$

Table 2.

Family and environmental exposure history of follow up cohorts.

	Low Sat N=439	High Sat N=479	CPAP N=474	Surfactant N=444
First degree relative with asthma - no. (%)	142 (31.8)	159 (32.4)	152 (31.3)	149 (33.0)
Family history of				
COPD, emphysema, etc - no. (%)	48 (10.7)	43 (8.8)	53 (10.9)	38 (8.4)
Food allergies - no. (%)	60 (14.4)	52 (11.3)	61 (13.5)	51 (11.9)
Inhaled allergies – no. (%)	140 (30.4)	129 (30.9)	136 (30.1)	133 (31.2)
Chronic Respiratory Disease no. (%)	7 (1.7)	4 (0.9)	1 (0.2)	10 (2.5)
Breast fed - no. (%)	7 (1.7)	4 (0.9)	1 (0.2)	10 (2.5)
Smoking in house - no. (%)	167 (37.4)	148 (30.1)	166 (34.2)	149 (33.0)
Spent time at daycare - no. (%)	189 (44.1)	186 (39.3)	189 (40.6)	186 (42.7)
Living with children under 12 - no. (%)	163 (41.5)	142 (33.2)	163 (38.4)	142 (35.8)
Pets in home- no. (%)	241 (61.3)	264 (61.7)	255 (60.1)	250 (63.0)
Flu vaccination- no. (%)	181 (40.5)	177 (36.1)	187 (38.5)	171 (37.8)
RSV prophylaxis - no. (%)	307 (78.1)	342 (80.1)	335 (79.0)	314 (79.3)
	281 (71.5)	313 (73.1)	308 (72.6)	286 (72.0)

Table 3. Respiratory outcomes for lower vs. higher oxygen saturation and early CPAP vs. intubation and surfactant cohorts at the 6 month interview and for the first 18-22 months corrected age (combined responses to the 6, 12 and 18-22 month interviews).

Primary Outcomes	**Low Sat**	**High Sat**	**ARR (95% CI)**	**p-value**	**CPAP**	**Surfactant**	**ARR (95% CI)**	**p-value**
Has your child's chest sounded wheezy or whistling more than twice in one week?								
6 months	94 (22.0)	129 (27.7)	0.73 (0.53, 1.01)	0.06	107 (23.2)	116 (26.9)	0.79 (0.58, 1.09)	0.16
6-22 months	203 (46.7)	233 (49.1)	0.92 (0.70, 1.22)	0.57	224 (47.7)	212 (48.2)	0.90 (0.68, 1.19)	0.47
Has your child had a cough for more than 3 days without a cold?								
6 months	63 (16.9)	76 (19.3)	0.84 (0.57, 1.22)	0.35	63 (16.2)	76 (20.2)	0.77 (0.53, 1.12)	0.17
6-22 months	127 (30.8)	141 (31.1)	1.01 (0.75, 1.37)	0.93	127 (28.4)	141 (33.7)	0.81 (0.60, 1.10)	0.18
Secondary Outcomes								
Symptoms								
Wheezing/whistling more than twice in one week or cough more than 3 days								
6 months†	162 (43.5)	195 (49.5)	0.78 (0.58, 1.05)	0.10	178 (45.8)	179 (47.5)	0.95 (0.70, 1.28)	0.72
6-22 months	276 (66.8)	316 (69.5)	0.87 (0.65, 1.18)	0.37	303 (67.8)	289 (68.7)	0.95 (0.70, 1.29)	0.74
Has your child's chest sounded wheezy or whistling?								
6 months	135 (36.3)	171 (43.4)	0.73 (0.54, 1.00)	<0.05	151 (38.8)	155 (41.1)	0.89 (0.66, 1.21)	0.47
6-22 months	245 (59.3)	286 (62.9)	0.85 (0.64, 1.13)	0.27	269 (60.2)	262 (62.2)	0.86 (0.64, 1.15)	0.31
Has your baby's chest sounded wheezy or whistling apart from colds?								
6 months	61 (16.4)	84 (21.3)	0.73 (0.50, 1.06)	0.10	66 (17.0)	79 (21.0)	0.77 (0.53, 1.11)	0.16
6-22 months	117 (28.4)	165 (36.3)	0.67 (0.49, 0.91)	0.01	129 (28.9)	153 (36.5)	0.68 (0.50, 0.92)	0.01
Illnesses								
Has your child had asthma, reactive airway disease or BPD exacerbation or flare-up diagnosed by a doctor?								
6 months†	51 (13.7)	62 (15.7)	0.84 (0.56, 1.27)	0.41	48 (12.3)	65 (17.2)	0.66 (0.44, 1.00)	<0.05
6-22 months†	140 (33.9)	158 (35.0)	1.01 (0.75, 1.37)	0.93	144 (32.2)	154 (36.8)	0.81 (0.60, 1.09)	0.16
Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?								
6 months	72 (19.4)	78 (19.8)	0.98 (0.67, 1.41)	0.90	70 (18.0)	80 (21.2)	0.82 (0.57, 1.19)	0.30
6-22 months	161 (39.0)	183 (40.4)	0.96 (0.72, 1.28)	0.79	167 (37.4)	177 (42.2)	0.81 (0.61, 1.09)	0.17
Any of asthma, reactive airway disease, BPD exacerbation or flare-up or bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor								
6 months	95 (25.5)	109 (27.7)	0.91 (0.65, 1.27)	0.58	96 (24.7)	108 (28.7)	0.81 (0.58, 1.13)	0.22
6-22 months	204 (49.4)	241 (53.1)	0.91 (0.69, 1.21)	0.52	213 (47.7)	232 (55.2)	0.71 (0.53, 0.95)	0.02

Has your child had croup diagnosed by a doctor?								
6 months††	9 (2.4)	11 (2.8)	0.87 (0.36, 2.08)	0.75	7 (1.8)	13 (3.5)	0.52 (0.21, 1.30)	0.15
6-22 months†	46 (11.2)	39 (8.6)	1.35 (0.84, 2.17)	0.21	40 (9.0)	45 (10.8)	0.77 (0.49, 1.23)	0.28
Health Services								
Has your child ever had to visit the doctor or Emergency Room for breathing or wheezing problems?								
6 months	167 (44.9)	188 (47.8)	0.82 (0.60, 1.11)	0.20	173 (44.6)	182 (48.3)	0.81 (0.60, 1.10)	0.18
6-22 months	292 (70.1)	319 (70.1)	0.98 (0.72, 1.34)	0.89	304 (68.0)	307 (72.9)	0.73 (0.53, 1.00)	<0.05
Has your child had to stay in a hospital overnight?								
6 months	105 (28.2)	118 (30.0)	0.89 (0.64, 1.23)	0.47	106 (27.3)	117 (31.0)	0.79 (0.57, 1.10)	0.17
6-22 months	169 (41.0)	199 (43.7)	0.90 (0.68, 1.20)	0.48	181 (40.7)	186 (44.3)	0.87 (0.66, 1.16)	0.35
Has your child had to stay in a hospital overnight for wheezing/breathing problems?								
6 months	69 (18.6)	73 (18.6)	0.98 (0.67, 1.44)	0.93	64 (16.5)	78 (27.0)	0.72 (0.49, 1.05)	0.09
6-22 months	129 (31.3)	141 (30.8)	1.04 (0.77, 1.40)	0.80	130 (29.1)	139 (33.1)	0.82 (0.61, 1.11)	0.21
Medications								
Treated with a diuretic medication?								
6 months†	27 (6.3)	24 (5.2)	1.29 (0.72, 2.32)	0.39	23 (5)	28 (6.5)	0.72 (0.40, 1.29)	0.27
6-22 months†	31 (7.1)	24 (5.0)	1.50 (0.85, 2.64)	0.16	24 (5.1)	31 (7.0)	0.68 (0.39, 1.20)	0.18
Treated with an inhaled steroid medication?								
6 months	51 (11.9)	53 (11.4)	1.12 (0.73, 1.71)	0.61	54 (11.7)	50 (11.6)	1.00 (0.66, 1.53)	0.99
6-22 months	112 (25.6)	129 (26.9)	0.97 (0.71, 1.32)	0.82	128 (27.1)	113 (25.5)	1.10 (0.80, 1.50)	0.56
Treated with a nebulized medication?								
6 months††	5 (1.2)	18 (3.9)	0.30 (0.11, 0.81)	0.02	13 (2.8)	10 (2.3)	1.18 (0.49, 2.86)	0.71
6-22 months†	29 (6.6)	42 (8.8)	0.73 (0.44, 1.22)	0.23	39 (8.3)	32 (7.2)	1.11 (0.67, 1.84)	0.69
Treated with a systemic steroid medication?								
6 months††	11 (2.6)	8 (1.7)	1.54 (0.61, 3.86)	0.36	12 (2.6)	7 (1.6)	1.45 (0.53, 3.91)	0.47
6-22 months	44 (10.1)	42 (8.8)	1.13 (0.71, 1.80)	0.62	48 (10.2)	38 (8.6)	1.22 (0.77, 1.95)	0.40
Treated with oxygen at home?								
6 months†	90 (24.3)	80 (20.3)	1.22 (0.83, 1.79)	0.31	80 (20.6)	90 (23.9)	0.82 (0.56, 1.21)	0.32
6-22 months	86 (25.1)	73 (20.0)	1.13 (0.71, 1.80)	0.14	94 (21.0)	106 (25.3)	0.80 (0.56, 1.15)	0.23
Family								
Have you had to change your plans because of your child's breathing problems?								
6 months	58 (15.5)	69 (17.5)	0.85 (0.57, 1.27)	0.43	50 (12.8)	77 (20.4)	0.58 (0.39, 0.87)	<0.01
6-22 months	139 (33.7)	170 (37.4)	0.87 (0.65, 1.17)	0.36	145 (32.4)	164 (39.0)	0.74 (0.55, 1.00)	<0.05

Results presented as number/total number (%); ARR – adjusted relative risk with adjustments for stratification factors (study center and gestational age group) and familial clustering. Where models did not converge, adjustments are limited to center and gestational age (†). If the two adjustment model failed to converge, unadjusted relative risks are reported (††).

30-Apr-2013

RE: MS# 2013-0756

Title: Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

Authors: Stevens, Timothy; Finer, Neil; Carlo, Waldemar; Szilagyi, Peter; Phelps, Dale; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Newman, Jamie; Das, Abhik; Do, Barbara; Schibler, Kurt; Rich, Wade; Newman, Nancy; Ehrenkranz, Richard; Peralta-Carcelen, Myriam; Vohr, Betty R.; Wilson-Costello, Deanne; Yolton, Kimberly; Heyne, Roy; Dusick, Anna; Evans, Patricia; Vaucher, Yvonne; Adams-Chapman, Ira; McGowan, Elisabeth; Bodnar, Anna; Pappas, Athina; Hintz, Susan; Acarregui, Michael; Fuller, Janell; Goldstein, Rikki; Bauer, Charles; O'Shea, Thomas; Myers, Gary; Higgins, Rosemary

Dear Dr. Stevens:

The editors of Pediatrics feel that your manuscript may have merit but would require substantial work before it could be seriously considered for publication. You are welcome to submit a revised manuscript, which will be sent out for peer review; referees may include past and new reviewers. Please be aware that fewer than half of such papers are ultimately accepted.

If you decide to resubmit this manuscript, you must address the concerns of the reviewers at the end of this e-mail. Your successful response to the critiques of the current reviewers does not guarantee acceptance of the manuscript, because new reviewers may be added for the revised paper and may have different concerns.

Comments from the editors

In addition to the reviewers' comments below, please address the following items from the editors:

1) It appears that not all the coauthors listed meet the authorship criteria.
The author list has been reviewed and revised. Please see the updated list and description of their responsibilities and contributions. Each author made a substantial contribution to the conception and design of the study, the data acquisition or analysis and interpretation as well as to drafting and revising the article for intellectual content and reviewing the submitted version of the manuscript.

2) Please address the ethical concerns about the original study.
In a letter dated June 4th, 2013, Lisa Buchanan, Compliance Officer for the Department of Health and Human Service's Office of Human Research Protection (OHRP), stated that "OHRP does not and never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent." In addition, she writes, "we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic. In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further action in studies involving similar designs until the process of producing appropriate guidance is completed." (http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf).

Based upon these comments, the following sentences have been added to the revised manuscript, "The SUPPORT Study and its design were deemed ethical by the Department of Health and Human Service's Office of Human Research Protection (OHRP). OHRP has initiated a public discussion of the adequacy of the written informed consent used in SUPPORT and similar trials of clinical practices that are within the range of standard of care at the time the research study was performed."

Comments from Reviewer: 1

The authors aimed to assess the long term respiratory outcomes from VLBW patients treated in the previously reported NICHD SUPPORT Trial. This is an important and valid research question, an appropriately large cohort, followed with rigorous methodology and the results are important:

In the Breathing Outcomes Study, authors have assessed the (b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

(b)(4),(b)(6)

Comments from Reviewer: 2

Thank you for the opportunity to review Stevens' and colleagues manuscript, "Respiratory outcomes of the early CPAP and pulse oximetry trial".

The NICHD SUPPORT Trial using a factorial design that randomized preterm infants to high versus low oxygen saturation targets and delivery room (early) CPAP or intubation. In the analysis of the CPAP vs. intubation arm of the study, the authors reported (b)(4),(b)(6)

(b)(4),(b)(6)

The authors of the "Breathing Outcome Study" explored longer term pulmonary outcome in these infants. The authors assessed (b)(4),(b)(6)

(b)(4),(b)(6)

Page 0384 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

From:	Luc Brion
To:	"Wally Carlo, M.D."; "doctorlevan@gmail.com"; "Das, Abhik"; "Wrage, Lisa Ann"; "Gantz, Marie"; Pablo Sanchez; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; "Finer, Neil"; "Barbara Stoll"
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Jackie LeVan's manuscript was submitted to Pediatrics.
Thanks a lot for all your help and collaboration
Best regards,
Luc

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To: Luc Brion; brionlp@aol.com
Subject: Thank you for your manuscript submission to Pediatrics

24-Jun-2013

Manuscript ID: 2013-2023
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Dear Dr. Luc Brion:

Thank you for submitting your article(s) to Pediatrics. This is an automated reply. If there are problems or questions, we will contact you by email.

If you submitted a new MANUSCRIPT, it will be screened and possibly peer-reviewed. The peer-review process may take eight weeks or more. If your manuscript is accepted, it will be published online. The Editors determine later if an accepted paper also will appear in the print edition. All accepted Case Reports are published online only.

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Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Journal:	*Pediatrics*
Manuscript ID:	Draft
Article Type:	Regular Article
Date Submitted by the Author:	n/a
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Keyword/Category:	Gestational age, Tracheal tube, Preterm infants, Mortality rates, cohort studies

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar A. Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

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Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

Revised 6/24/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
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Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 248 words
Article length: 2,288 words

Abstract

Introduction

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers.

Methods:

This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

Conclusions:

After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen

saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.[1,2] Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variable:

The primary outcome variable was ETI in DR.

Secondary outcome variables:

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of postmenstrual age (PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Other secondary outcomes included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal

corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[6] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16] Since we did not adjust p value for multiple comparisons, all secondary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion

information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For the most important secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 3). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 3). In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average

number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Additional unadjusted comparisons are shown in table 4. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study

sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. Limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,[21] more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have

changed based on other studies, e.g., studies on antenatal steroids,[22] treatment and prophylaxis of patent ductus arteriosus,[23-25] synchronized nasal intermittent positive-pressure ventilation,[26] prevention of central line-associated bloodstream infections,[27,28] or nutrition.[29] DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[30] Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI , ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams): mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcome[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001

Abbreviation: RR, relative risk
[1] presented as n (%)
[2] unadjusted p-value from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

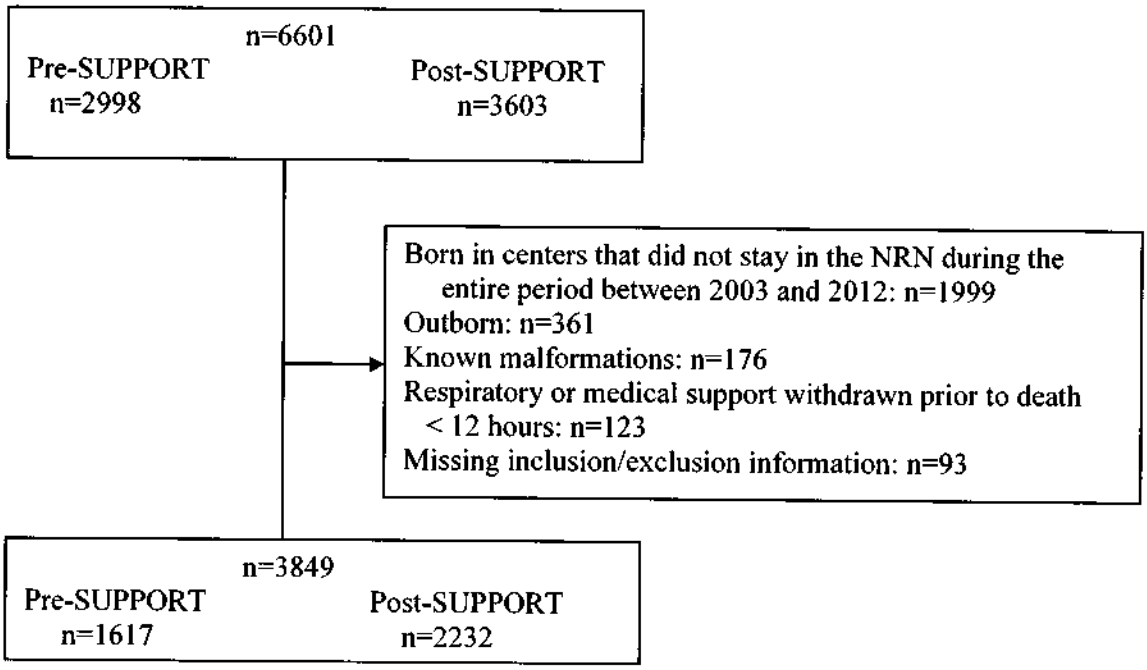
[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

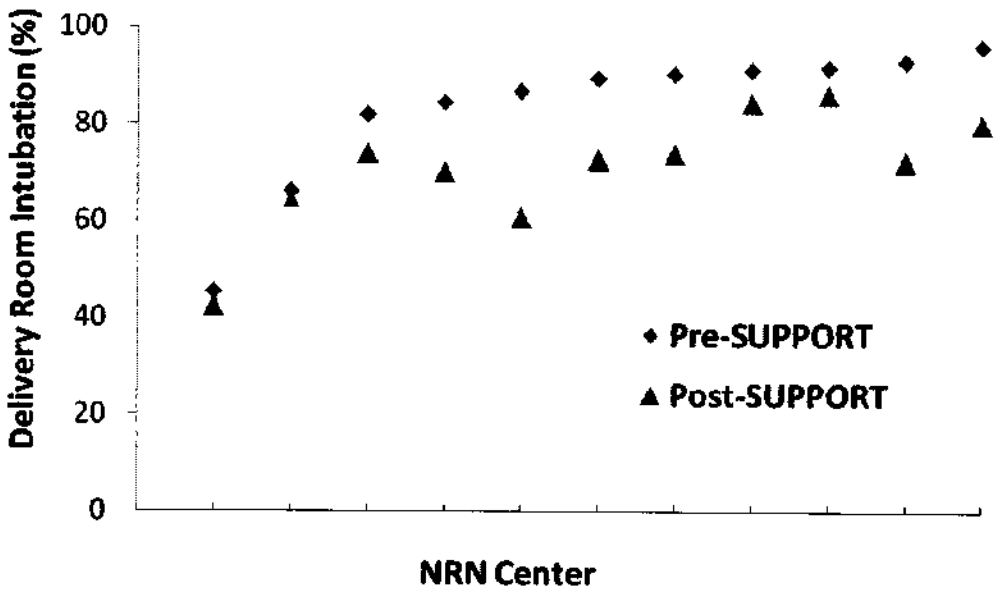
[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1



The American Academy of Pediatrics, 141 Northwest Point Blvd., Elk Grove Village, IL 60007

Figure 2



From: Luc Brion
To: adas@rti.org; Gantz, Marie; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; Barbara Stoll
Subject: FW: Final version of Jackie LeVan"s paper, ready for submission
Date: Monday, June 24, 2013 5:09:47 PM

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, June 24, 2013 3:13 PM
To: Luc Brion
Subject: RE: Final version of Jackie LeVan's paper, ready for submission

Looks good.
FYI I will be working away from the office tomorrow so I will return emails on Wednesday.
Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, June 24, 2013 3:54 PM
To: Wrage, Lisa Ann; doctorlevan@gmail.com; Wally Carlo, M.D.; Roy Heyne; Finer, Neil
Subject: Final version of Jackie LeVan's paper, ready for submission

Here is the final version, in which

1. I edited the current manuscript to include the main findings in Jackie's other study (ref 21). We need to mention that we cannot exclude that the change in the proportion of ETI in the NRN could have occurred during or before publication of SUPPORT.
2. I shortened the title of our manuscript because Pediatrics submission software wants it shorter.

Since Jackie's other study was accepted today for publication in Pediatrics pending minor revisions I will mention in my letter that we will change reference 21 to the manuscript in press if and when it gets accepted for publication.

Best regards,

Luc

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, June 24, 2013 10:49 AM
To: Luc Brion
Cc: doctorlevan@gmail.com
Subject: RE: Updated version of Jackie LeVan's paper, ready for submission

Great! I think you can submit!

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, June 24, 2013 11:46 AM
To: Wrage, Lisa Ann
Cc: doctorlevan@gmail.com
Subject: RE: Updated version of Jackie LeVan's paper, ready for submission

Thanks, Lisa

I did that change.

Here is the revised document.

Luc

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, June 24, 2013 10:04 AM
To: Luc Brion
Subject: RE: Updated version of Jackie LeVan's paper, ready for submission

Hi Luc,

The paper sounds good. There is one repeated sentence on page 9: "Since we did not adjust p value for multiple comparisons……". You've said this in the stat methods section plus you discuss in the discussion, so I think that this one could come out.

Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, June 21, 2013 10:34 PM
To: Wally Carlo, M.D.; doctorlevan@gmail.com; Das, Abhik; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Barbara Stoll
Subject: RE: Updated version of Jackie LeVan's paper, ready for submission

Wally:

Thanks a lot for your comments.

I accepted all your comments and changes including rebuilding the document with one primary outcome.

I attach two versions: one tracked and one clean version.

Dear Colleagues:

Please review and let me know if you have any comments.

Best regards,

Luc

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, June 21, 2013 6:08 PM
To: Luc Brion; doctorlevan@gmail.com; Das, Abhik; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Barbara Stoll
Subject: RE: Updated version of Jackie LeVan's paper, ready for submission

Hi Luc and Jackie:

Excellent. I have made tracked suggestions.

I think it is important not to imply causality so I have made several changes related to that.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Friday, June 21, 2013 4:59 PM
To: doctorlevan@gmail.com; Das, Abhik; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Barbara Stoll; Luc Brion
Subject: Updated version of Jackie LeVan's paper, ready for submission

Here is a revised version, including several comments from Lisa Wrage and Roy Heyne.
If you have any comments please email me by 6/26/13.
The plan is to submit this manuscript to Pediatrics on 6/27/13.
Thanks for your collaboration and best regards,
Luc

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 24, 2013 2:53 PM
To: Kaeser, Lisa (NIH/NICHD) [E]; Whitfield, Michelle D. (NIH/OD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: RE: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study

Thanks!

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
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Phone: 301-496-3454
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From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Monday, June 24, 2013 2:49 PM
To: Whitfield, Michelle D. (NIH/OD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: RE: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study

We really appreciate that, thanks!

Lisa Kaeser, J.D.
Director, Office of Legislation and Public Policy
Eunice Kennedy Shriver National Institute
of Child Health and Human Development/NIH
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Building 31, Room 2A03
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From: Whitfield, Michelle D. (NIH/OD) [E]
Sent: Monday, June 24, 2013 2:49 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: RE: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study

Thank you, Lisa!
I will reassign this to OCPL and ask that they work with NICHD (for factual information about the trial) to prepare the response and I will send a necessary action assignment to NICHD (no due date) asking that you work with OCPL.

Thanks again!

Michelle

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Monday, June 24, 2013 2:25 PM
To: Whitfield, Michelle D. (NIH/OD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: FW: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
Importance: High

Hi Michelle –

No one here, including Dr. Guttmacher, is familiar with the circumstances about how Dr. Natanson was asked not to participate in the webinar that is mentioned in the incoming letter. The letter quotes Renate Myles telling the authors why he could not participate. Particularly since this is (b)(5) (b)(5) (b)(5) So we are asking that the response be reassigned to OCPL. We are happy to provide factual information about the SUPPORT trial, as needed.

I'm here this afternoon if you need to discuss? Sorry for the delay, I just had a chance to talk with Dr. Guttmacher.

Thanks!

Lisa

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From: Ott, Sandra (NIH/NICHD) [E]
Sent: Thursday, June 20, 2013 2:11 PM
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
Importance: High

Lisa,

This originally came in as an FYI on June 13. Today this was assigned to NICHD to prepare a draft for the Secretary's Signature and is due by June 27. We are to prepare a draft response for the Secretary's signature and a Summary Statement. We are to return to ES in DDRMS by COB June 27. The PA on this is Michelle Whitfield.

Sandy.

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
Sent: Thursday, June 20, 2013 12:59 PM
To: Brown, Crystal (NIH/NICHD) [C]; Ott, Sandra (NIH/NICHD) [E]; Wood, Vandora (NIH/CIT) [C]
Subject: WF 322943 - Create and Assemble Response (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

You have received a task notification requiring your attention.

Additional instructions are included on the task form, please click the following link to open the task:

Task

Please do not reply to this email, this is an automated message.

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Work Folder Information
Work Folder: WF 322943
Process: IC Response CreationWF 322943
Due Date: June 27, 2013
Program Analyst: Whitfield, Michelle D. (NIH/OD) [E]
WF Subject: Letter from Public Citizen's Health Research Group complaining about NIH expert that was silenced because he previously raised concerns about the SUPPORT study
IC:NICHD
From: Carome, Michael;
To: Sebelius, Kathleen;Collins, Francis;
Remarks: Assigned to NICHD for response creation to prepare a draft Sec Sig by June 27. Please prepare a draft response for the Secretary's signature and a Summary Statement and return to ES by c.o.b. June 27. Thank you.

From: Luc Brion
To: Wally Carlo, M.D.; (b)(6) @gmail.com; Das, Abhik; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Barbara Stoll
Subject: RE: Updated version of Jackie LeVan"s paper, ready for submission
Date: Friday, June 21, 2013 10:33:45 PM
Attachments: Jackie LeVan Manuscript NRN 06-21-13 clean prim revwc LPB.docx
Jackie LeVan Manuscript NRN 06-21-13 prim revwc LPB.docx

Wally:
Thanks a lot for your comments.
I accepted all your comments and changes including rebuilding the document with one primary outcome.
I attach two versions: one tracked and one clean version.

Dear Colleagues:
Please review and let me know if you have any comments.

Best regards,
Luc

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, June 21, 2013 6:08 PM
To: Luc Brion; doctorlevan@gmail.com; Das, Abhik; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Barbara Stoll
Subject: RE: Updated version of Jackie LeVan's paper, ready for submission

Hi Luc and Jackie:

Excellent. I have made tracked suggestions.

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Subject: Updated version of Jackie LeVan's paper, ready for submission

Here is a revised version, including several comments from Lisa Wrage and Roy Heyne.
If you have any comments please email me by 6/26/13.
The plan is to submit this manuscript to Pediatrics on 6/27/13.
Thanks for your collaboration and best regards,
Luc

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UT Southwestern Medical Center
The future of medicine, today.

Changes in Therapy and Outcome After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar A. Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

Revised 6/21/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 248 words
Article length: 2,243 words

Abstract

Introduction
The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen

saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.[1,2] Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variable:

The primary outcome variable was ETI in DR.

Secondary outcome variables:

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of postmenstrual age (PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Other secondary outcomes included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal

corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[6] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16] Since we did not adjust p value for multiple comparisons, all secondary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion

information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For the most important secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 3). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. Since we did not adjust p value for multiple comparisons, all secondary analyses should be considered as exploratory.

The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 3). In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI

0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Additional unadjusted comparisons are shown in table 4. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study

sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. Limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the

American Academy of Pediatrics and American Heart Association.[29] Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI , ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcome[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001

Abbreviation: RR, relative risk
[1] presented as n (%)
[2] unadjusted p-value from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center
[4] adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second period.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

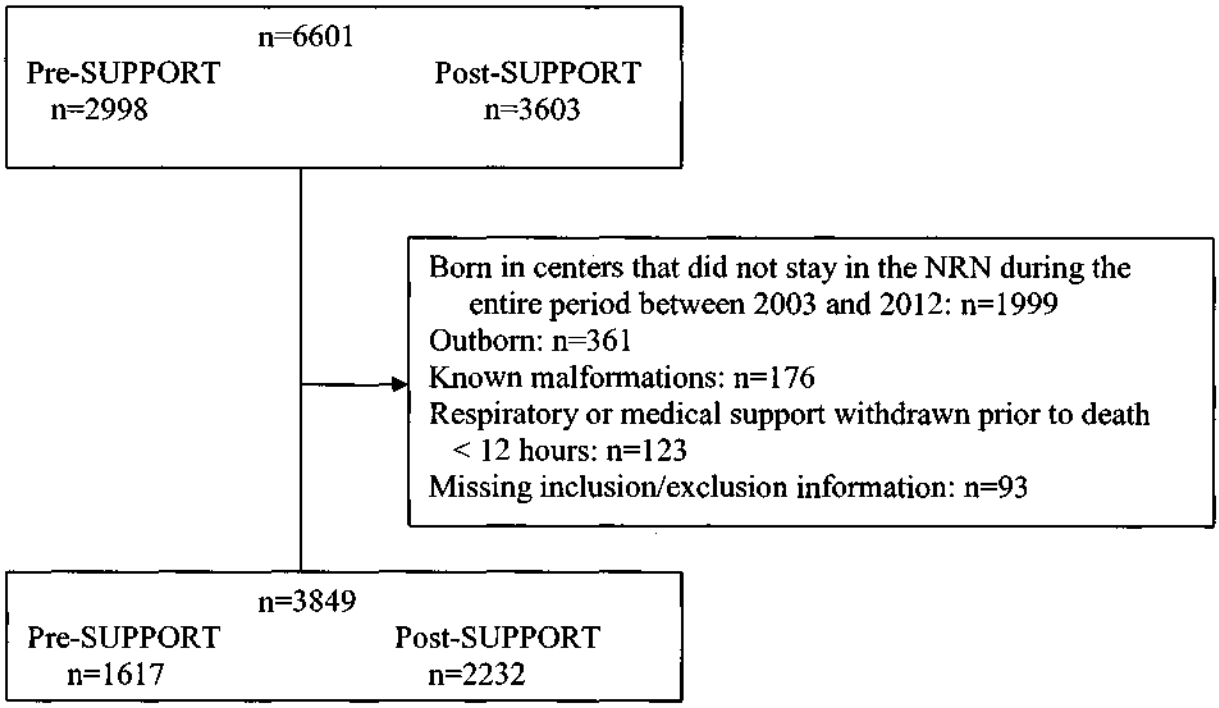
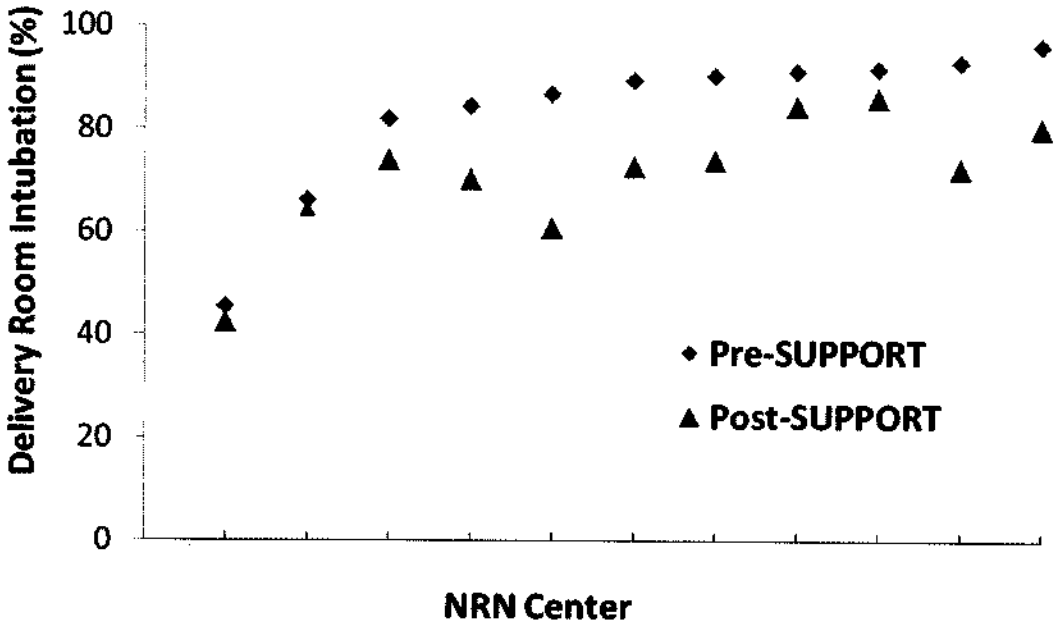


Figure 2



Changes in Therapy and Outcome After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation, GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

Revised 6/2~~1~~8/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
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Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 24~~5~~45 words
Article length: 2,243~~178~~ words

Abstract

Introduction
The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the currentis study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcomes wasere DR intubation. The most important secondary outcomes were, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

~~Discussion:~~
~~This study is limited by its observational before/after design; therefore we do not claim that changes observed after this trial were caused by publication of the results of SUPPORT.~~

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Comment [WC1]: I would include the actual RRs and CIs here.

Comment [WC2]: This discussion is not needed here.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) ~~trial~~ was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The

risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was ~~there was a~~ temporally associated~~ion~~ with changes ~~the impact of the results of the SUPPORT trial~~ ion clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT- there would be a lower~~decrease in~~ proportion of ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. -These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT ~~trial~~ was followed by changes in several other neonatal processes of care and outcomes.

Comment [WC3]: One cannot assume it was the "impact" of SUPPORT. I

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT

Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohortsepochs.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.[1,2] Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode

of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables ~~was~~were ETI in DR.~~, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial. BPD was defined by oxygen use at 36 weeks of postmenstrual age (PMA). Severe ROP was defined as ROP surgery or retinal detachment.~~

Comment [WC4]: It is preferable to state one primary outcome and the others as secondary outcomes rather than many primary outcomes.

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Secondary outcome variables:

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of postmenstrual age (PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Other sSecondary outcomes included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis,

intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[6] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for primary outcomes and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment,

late onset sepsis and intrauterine growth restriction.[7-16] Since we did not adjust p value for multiple comparisons, all secondary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first ~~epoch~~period (pre-SUPPORT) to the second ~~epoch~~period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first ~~epoch~~period.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group. The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged

rupture of membranes (24.1% vs. 27.5%, p=0.017) in the ~~p~~Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

Comment [WCS]: Best to use or not use uppoer case for both groups.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For the most important secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of ~~and~~ the risk of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 3). The adjusted risk of ~~DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91),~~ BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT ~~(Table 2)~~. Since we did not adjust p value for multiple comparisons, all secondary ~~these~~ analyses should be considered as exploratory.

~~Secondary outcomes are shown in Tables 3 and 4.~~ The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 3). In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The a~~A~~verage number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT ~~(Table 3)~~.

Additional u~~U~~nadjusted comparisons are shown in table 4. Several differences were observed between the two ~~epoch~~periods. ~~Since we did not adjust p-value for multiple comparisons, these analyses should be considered as exploratory.~~

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first ~~epoch~~period and the change in proportion of intubations in the DR from the first to the second ~~epoch~~period was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks GA -born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI- and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two ~~epoch~~periods. Limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[29] Several processes of

care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI , ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers was lowerdecreased following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also wasdecreased significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The aAverage number of ventilator days among survivors was lowerdecreased after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT ~~epoch~~period

for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes[1]

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Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
~~BPD or death at 36 weeks~~	~~970 (60.0)~~	~~1199/2213 (54.2)~~	~~0.0003~~	~~0.94 (0.89-0.99)~~	~~0.02~~
~~Severe ROP or death~~	~~515/1581 (32.6)~~	~~559/2165 (25.8)~~	~~<0.0001~~	~~0.81 (0.73-0.89)~~	~~<0.0001~~
~~Death before discharge~~	~~358/1614 (22.2)~~	~~393/2196 (17.9)~~	~~0.001~~	~~0.86 (0.76-0.98)~~	~~0.02~~

Abbreviations: ~~BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity;~~ RR, relative risk

[1] presented as n (%)

[2] unadjusted p-values from Chi-Square tests

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

[4] adjusted p-values from robust Poisson model

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p-value[4]
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.

[4] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

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Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second ~~epoch~~period.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

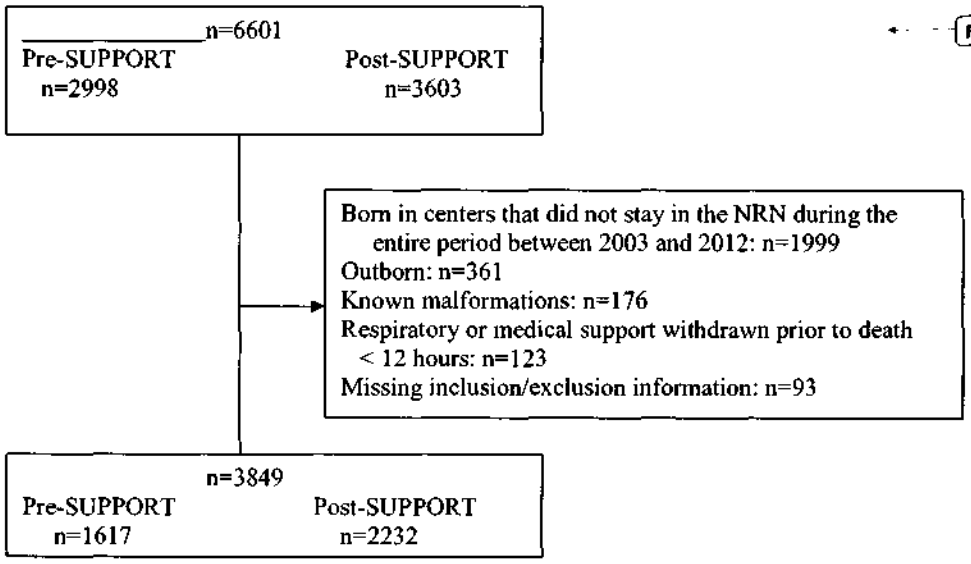

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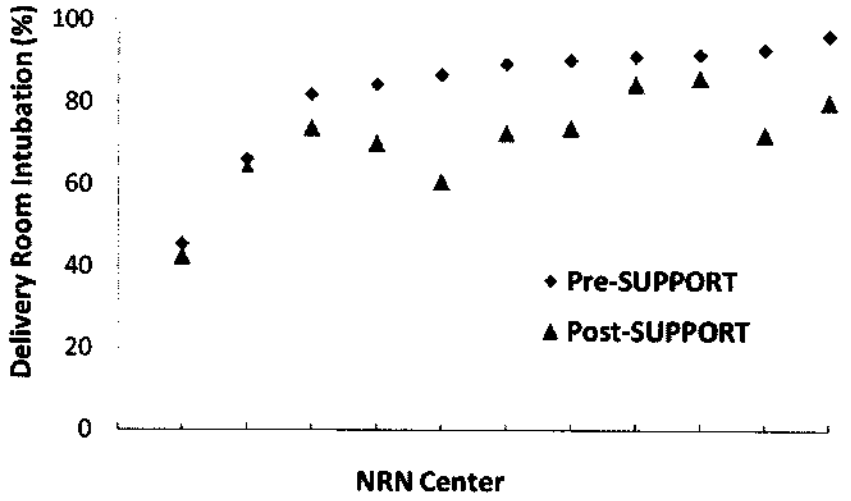
Figure 2



From: Luc Brion
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Subject: Updated version of Jackie LeVan"s paper, ready for submission
Date: Friday, June 21, 2013 5:59:16 PM
Attachments: Jackie LeVan Manuscript NRN 06-21-13 clean rev.docx

Here is a revised version, including several comments from Lisa Wrage and Roy Heyne.
If you have any comments please email me by 6/26/13.
The plan is to submit this manuscript to Pediatrics on 6/27/13.
Thanks for your collaboration and best regards,
Luc

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Changes in Therapy and Outcome After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

Revised 6/18/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
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Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 245 words
Article length: 2,178 words

Abstract

Introduction
The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one.

Discussion:
This study is limited by its observational before/after design; therefore we do not claim that changes observed after this trial were caused by publication of the results of SUPPORT.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either CPAP initiated in the DR and protocol-driven limited ventilation begun in the DR, or ETI with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine the impact of the results of the SUPPORT

trial on clinical practice, specifically the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a decrease in proportion of ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT trial was followed by changes in several other neonatal processes of care and outcomes.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients

born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both epochs.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT. [1,2] Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were ETI in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in

the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial. BPD was defined by oxygen use at 36 weeks of postmenstrual age (PMA). Severe ROP was defined as ROP surgery or retinal detachment.

Secondary outcome variables:

Secondary outcomes included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[6] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the

unadjusted tests, and that preceded the outcome. The models for primary outcomes and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR ETI and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2).

Secondary outcomes are shown in Tables 3 and 4. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4. Several differences were observed between the two epochs. Since we did not adjust p value for multiple comparisons, these analyses should be considered as exploratory.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first epoch and the change in proportion of intubations in the DR from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two

epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[29] Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI , ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT trial. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after SUPPORT.

Since this is an observational study, it is impossible to determine the contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second epoch.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

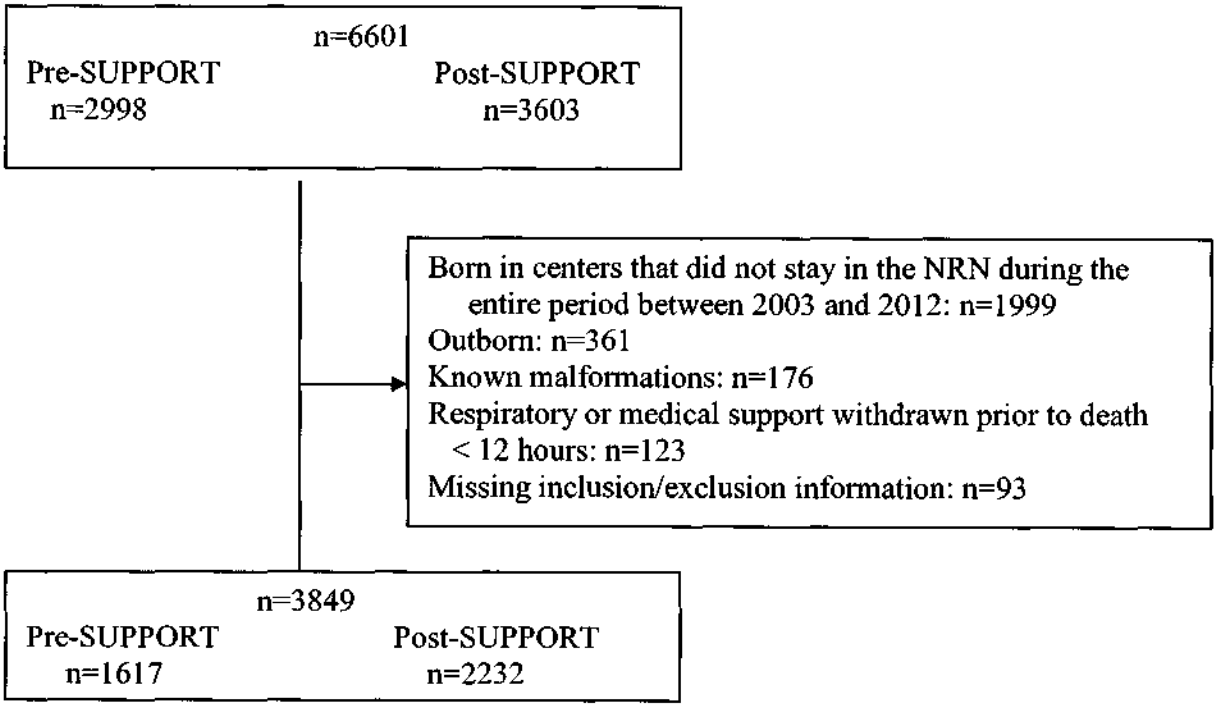
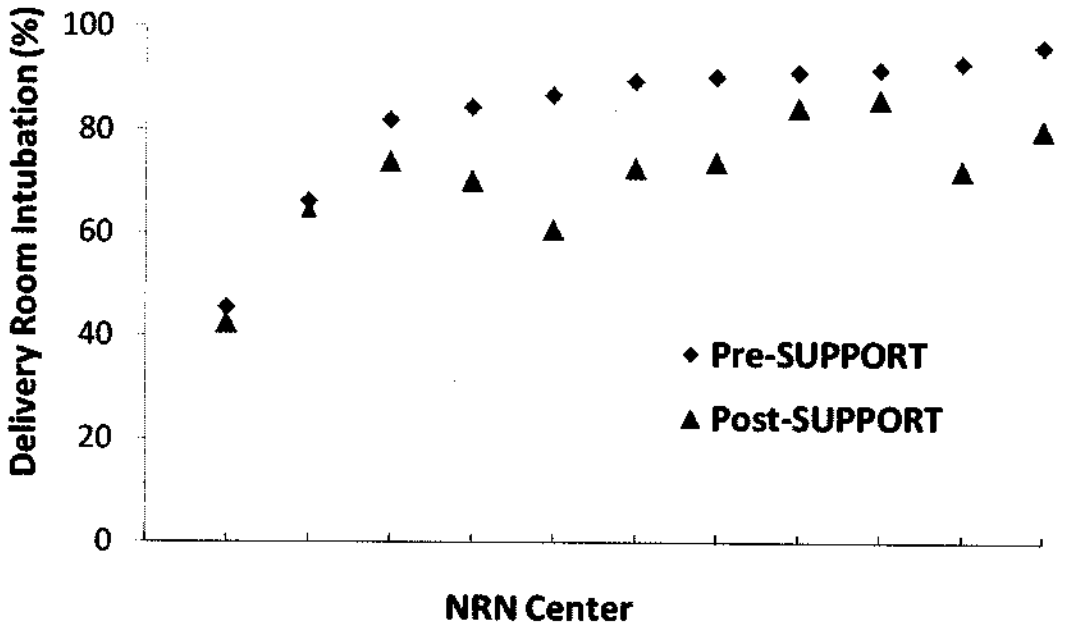


Figure 2



From: Higgins, Rosemary (NIH/NICHD) [E]
To: Kaeser, Lisa (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: Re: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
Date: Friday, June 21, 2013 10:07:51 AM

Ok
Thanks

Sent from my iPhone

On Jun 21, 2013, at 4:25 AM, "Kaeser, Lisa (NIH/NICHD) [E]" <kaeserl@mail.nih.gov> wrote:

> Please don't worry about it -- I just wanted to know if you knew of him. We'll take care of it. You deserve a break!!!!
>
> Lisa Kaeser, J.D.
> Director, Office of Legislation and Public Policy
> Eunice Kennedy Shriver National Institute
> of Child Health and Human Development/NIH
> 31 Center Drive, MSC 2425
> Building 31, Room 2A03
> Bethesda, MD 20892
> 301-496-0536
> kaeserl@mail.nih.gov
>
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E]
> Sent: Thursday, June 20, 2013 9:31 PM
> To: Kaeser, Lisa (NIH/NICHD) [E]
> Cc: Spong, Catherine (NIH/NICHD) [E]
> Subject: Re: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
>
> Hi
> I do not know dr. Natanson and was unaware of the request. If needed I can call in the late - we are leaving (b)(6) and will have cell phone service in (b)(6)
>
> Let me know
>
> Sent from my iPhone
>
> On Jun 20, 2013, at 10:42 AM, "Kaeser, Lisa (NIH/NICHD) [E]" <kaeserl@mail.nih.gov> wrote:
>
>> Hi – I believe Rose is out this week? We just received this control (as Sandy pointed out, previously it was just sent to us FYI, but now they want us to draft the response for the Secretary). It's due next Thursday to Building 1, but Alan would like to see the response before it goes over.
>>
>> I don't have any of the facts about Dr. Natanson, so I can't even start a draft. Can you help draft, or steer me in the right direction, please?
>>
>> Sorry!
>>
>> Lisa
>>

>> Lisa Kaeser, J.D.
>> Director, Office of Legislation and Public Policy Eunice Kennedy
>> Shriver National Institute of Child Health and Human Development/NIH
>> 31 Center Drive, MSC 2425
>> Building 31, Room 2A03
>> Bethesda, MD 20892
>> 301-496-0536
>> kaeserl@mail.nih.gov<mailto:kaeserl@mail.nih.gov>
>>
>> From: Ott, Sandra (NIH/NICHD) [E]
>> Sent: Thursday, June 20, 2013 2:11 PM
>> To: Kaeser, Lisa (NIH/NICHD) [E]
>> Cc: Ott, Sandra (NIH/NICHD) [E]
>> Subject: WF 322943 - Draft Response due COB 06/27/2013 - SUPPORT Study
>> Importance: High
>>
>> Lisa,
>>
>> This originally came in as an FYI on June 13. Today this was assigned to NICHD to prepare a draft for the Secretary's Signature and is due by June 27. We are to prepare a draft response for the Secretary's signature and a Summary Statement. We are to return to ES in DDRMS by COB June 27. The PA on this is Michelle Whitfield.
>>
>> Sandy.
>>
>> From: EDRMS_NO_REPLY@mail.nih.gov<mailto:EDRMS_NO_REPLY@mail.nih.gov>
>> [mailto:EDRMS_NO_REPLY@mail.nih.gov]
>> Sent: Thursday, June 20, 2013 12:59 PM
>> To: Brown, Crystal (NIH/NICHD) [C]; Ott, Sandra (NIH/NICHD) [E]; Wood,
>> Vandora (NIH/CIT) [C]
>> Subject: WF 322943 - Create and Assemble Response (CC)
>>
>>
>> To whom it may concern:
>>
>> Message from the Director's Document and Records Management System
>> (DDRMS)
>>
>> You have received a task notification requiring your attention.
>>
>> Additional instructions are included on the task form, please click the following link to open the task:
>>
>> Task<https://nihedrmsprdapp1.nih.gov/taskspace?objectId=1b003a998397b2
>> 71&appname=nihddrms&docbase=NIH_DDRMS>
>>
>> Please do not reply to this email, this is an automated message.
>>
>> If you have concerns please contact the NIH Help Desk at (301) 496-4357.
>>
>> Work Folder Information
>> Work Folder: WF 322943
>> Process: IC Response CreationWF 322943 Due Date: June 27, 2013 Program
>> Analyst: Whitfield, Michelle D. (NIH/OD) [E] WF Subject: Letter from
>> Public Citizen's Health Research Group complaining about NIH expert
>> that was silenced because he previously raised concerns about the
>> SUPPORT study IC:NICHD
>> From: Carome, Michael;
>> To: Sebelius, Kathleen;Collins, Francis;

>> Remarks: Assigned to NICHD for response creation to prepare a draft Sec Sig by June 27. Please prepare a draft response for the Secretary's signature and a Summary Statement and return to ES by c.o.b. June 27. Thank you.
>> <322943 - Control Sheet.pdf>
>> <322943 - Incoming - 1 Support Study and NIH Censorship of Dissenting
>> Opinions.pdf>
>> <322943 - Incoming - 1a 130613 Letter to HHS Secretary.pdf>

From: Luc Brion
To: Myra Wyckoff; (b)(6) @gmail.com; Wrage, Lisa Ann; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne; Mambarambath Jaleel; Pablo Sanchez; Wally Carlo, M.D.; Barbara Stoll; Finer, Neil; Luc Brion
Subject: Revised and hopefully final version of Jackie LeVan"s manuscript
Date: Thursday, June 20, 2013 6:42:18 PM
Attachments: Jackie LeVan Manuscript NRN 06-20-13.doc
Jackie LeVan Manuscript NRN 06-20-13 clean.doc

Here is the revised and hopefully final version of Jackie LeVan's manuscript, with several changes by Lisa Wrage.

So far all responses I have received support me sending the manuscript to Pediatrics without a survey and without another network.

If you have any additional comment please let me know.

Unless I hear otherwise by 6/26/13, I will submit the manuscript to Pediatrics next week Thursday 6/27/13.

Thanks a lot for your collaboration and thanks your help.

Best regards,

Luc

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Changes in Therapy and Outcome After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

Revised 6/20/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 245 words
Article length: 2,247 words

Abstract

Introduction
The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers. .

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one.

Discussion:
This study is limited by its observational before/after design; therefore we do not claim that changes observed after this trial were caused by publication of the results of SUPPORT.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either CPAP initiated in the DR and protocol-driven limited ventilation begun in the DR , or ETI with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine the impact of the results of the SUPPORT

trial on clinical practice, specifically the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a decrease in proportion of ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. These included risk of death or BPD death or severe ROP at the time of discharge and death before discharge. We also examined if publication of SUPPORT trial was followed by changes in risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP, death before discharge and several other neonatal processes of care and outcomes.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Assuming 10% exclusions, the first 2-year cohort was estimated to yield approximately 2400 infants for analysis. We collected data for 2 years before SUPPORT and 3 years after SUPPORT because the number of patients in GDB, corrected for the number of centers that had participated in SUPPORT and remained in the NICHD NRN during the entire period, decreased over time. Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both epochs.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT. [1,2]. Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. care.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode

of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were ETI in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial. BPD was defined by oxygen use at 36 weeks of postmenstrual age (PMA). Severe ROP was defined as ROP surgery or retinal detachment.

Secondary outcome variables:

Secondary outcomes included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[6] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. The models for primary outcomes and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not postnatal variables, to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR ETI and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2).

Secondary outcomes are shown in Tables 3 and 4. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first epoch and the change in proportion of intubations in the DR from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR ETI decreased significantly only in centers with a high baseline proportion. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96

and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes. The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus

arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[29] Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI , ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT trial. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after SUPPORT.

Since this is an observational study, it is impossible to determine the contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second epoch.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

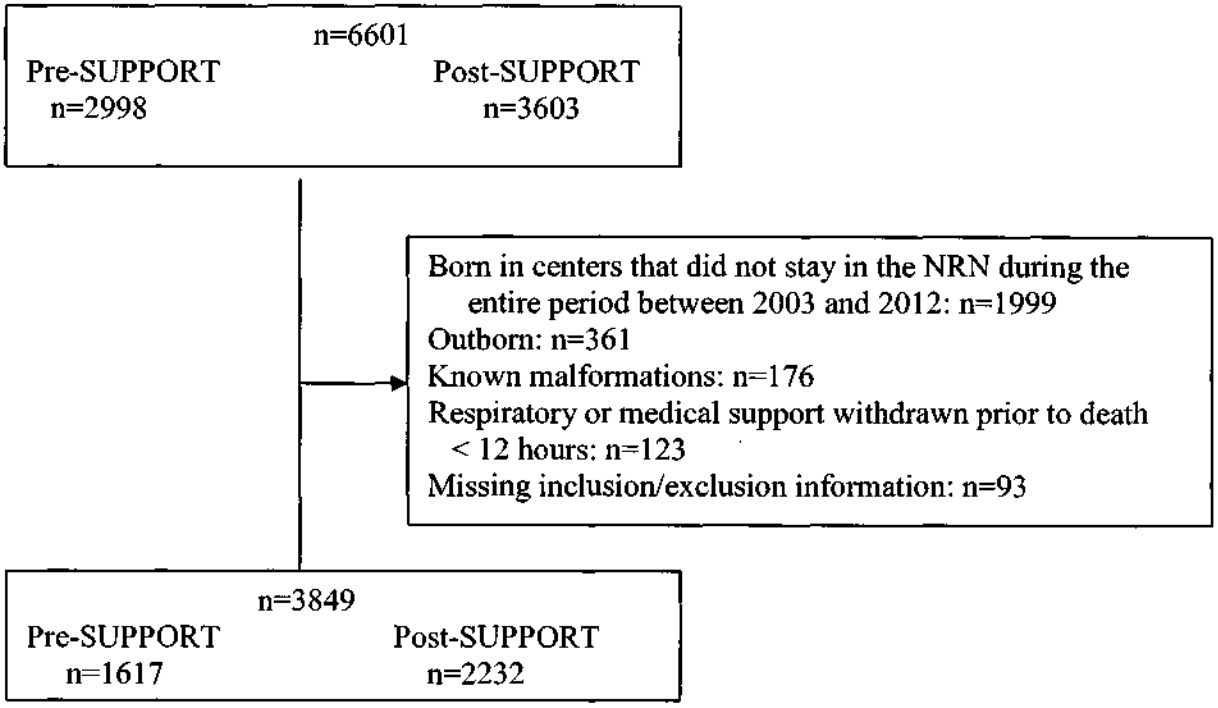
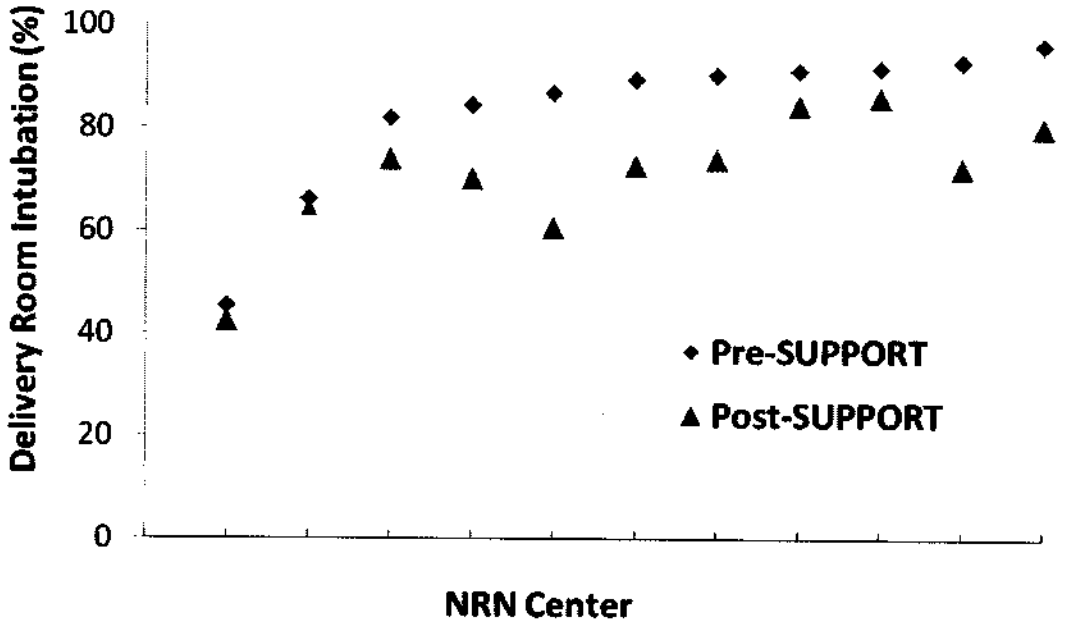


Figure 2



Changes in Therapy and Outcome After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

Revised 6/18/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
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Abstract length: 245 words
Article length: 2,241 words

Abstract

Introduction
The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers. .

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one.

Discussion:
This study is limited by its observational before/after design; therefore we do not claim that changes observed after this trial were caused by publication of the results of SUPPORT

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either CPAP initiated in the DR and protocol-driven limited ventilation begun in the DR , or ETI with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum ($24^{0/7}$ weeks to $25^{6/7}$ weeks) and 751 in the higher stratum ($26^{0/7}$ weeks to $27^{6/7}$ weeks).[1,2] The results of the SUPPORT trial were published in May 2010.[1,2] The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.[1] In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, t~~T~~he risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group. The objective of this study was to determine the impact of the results of the SUPPORT

Comment [w1]: I am not sure why you changed this. The paper states that this was true in the low GA group (24-25 weeks), but not for the higher GA group. The tables in the paper show that there was no difference overall in death at 36 weeks. (p=.09).

Comment [L2]: This was a change made by the reviewer. You are right, we must leave it the way it was.

trial on clinical practice, specifically the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a decrease in proportion of ETI in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks changed after SUPPORT. These included risk of death or BPD death or severe ROP at the time of discharge and death before discharge. We also examined if publication of SUPPORT trial was followed by changes in risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP, death before discharge and several other neonatal processes of care and outcomes.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Assuming 10% exclusions, the first 2-year cohort was estimated to yield approximately 2400 infants for analysis. We collected data for 2 years before SUPPORT and 3 years after SUPPORT because the number of patients in GDB, corrected for the number of centers that had participated in SUPPORT and remained in the NICHD NRN during the entire period, decreased over time. Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both epochs.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.[1,2]. Specifically, eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. care.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode

of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were ETI in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial. BPD was defined by oxygen use at 36 weeks of postmenstrual age (PMA). Severe ROP was defined as ROP surgery or retinal detachment.

Secondary outcome variables:

Secondary outcomes included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. ~~These~~ All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)[6] as well as additional covariates that were significantly different by study group ($p < 0.10$) in the unadjusted tests, and that preceded the outcome. ~~. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes.~~ The models for p~~P~~rimary outcomes and all secondary outcomes, with the exception of BPD, ~~were adjusted for~~included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not ~~for~~ postnatal variables, to which some infants may not have been exposed before the outcome took place. ~~We created a model specific for BPD, considering the following potential covariates:~~ The model for BPD contained these same additional variables as well as intubation in the DR, surfactant,

FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, $p<0.0001$), maternal hypertension (27.4% vs. 19.9%, $p<0.0001$), maternal diabetes (5.4% vs. 2.6%, $p<0.0001$), cesarean section delivery (66.3% vs. 62.1%, $p=0.0078$), and prolonged

rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR ETI and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2).

Secondary outcomes are shown in Tables 3 and 4. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first epoch and the change in proportion of intubations in the DR from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.18).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR ETI decreased significantly only in centers with a high baseline proportion. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes. The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for

informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[29] Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies.

Conclusion

After adjustment for baseline variables, the proportion of DR ETI , ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT trial. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risk of death at 36 weeks PMA and of BPD did

not change significantly. Average ventilator days among survivors decreased after SUPPORT.

Since this is an observational study, it is impossible to determine the contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second epoch.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

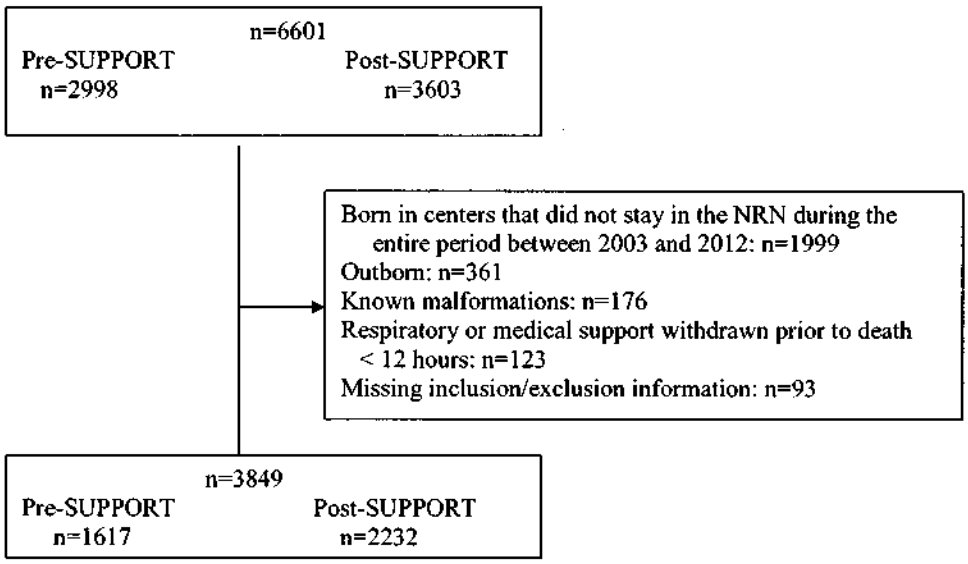
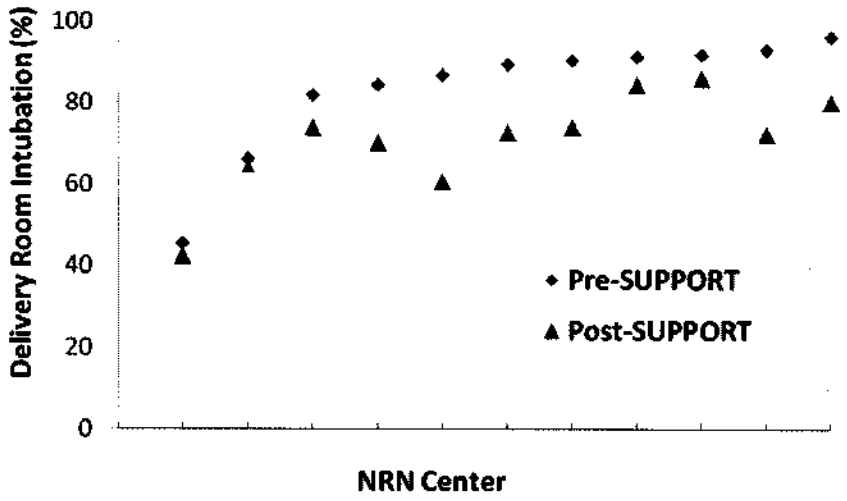


Figure 2



From: Kennedy, Kathleen A
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das (adas@rti.org)
Subject: RE: Resubmission of ROP Secondary Paper
Date: Thursday, June 20, 2013 3:57:52 PM

I'm happy to have Rose's input. If there are decisions to be made regarding how to handle an error that was uncovered in the primary outcome for the SUPPORT trial, that should be handled but the full SUPPORT subcommittee. I don't see how the scientifically ethical responsible approach would be to ignore it, and present something that repeats the error in a new publication, because we have "data lock". Changing one outcome will not change the effect or the effect size for the parent trial. We might consider checking all the subjects for consistency with the GDB question regarding the ROP outcome. Then the subcommittee can make a decision about how to proceed.

Either way, it's an opportunity to try to avoid this problem in the Inositol trial.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, June 20, 2013 12:28 PM
To: Kennedy, Kathleen A
Subject: RE: Resubmission of ROP Secondary Paper

Hi Kathleen,

The issue of how to deal with the miscoded infant will have to be discussed with Rose. She's away at present, so we'll just have to wait.

It is a very sensitive issue. The answer I got back from Abhik was not what I expected. He and Rose may have to deliberate.

You might consider what kind of a footnote you would write to the revised Figure 1. Putting it in words would probably help us all decide if we can live with the proposed change.

(b)(6) I am sorry that I will be away as this is worked out. I'll try to get back to is as soon as feasible upon my return.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, June 13, 2013 12:58 PM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Phelps, Dale; Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD); Archer, Stephanie
Subject: Resubmission of ROP Secondary Paper

This was not accepted by Pediatrics. No real substantive criticisms. I'm circulating a revision that's prepared for submission to J Perinatol. Dale and Lisa and Rose and I have made a few changes based on the reviewers' comments. Things that have been changed (mostly clarifications, not changes) since the Pediatrics submission are in green text. There's one sentence that might need to be changed when we get to the bottom of some questions about the data for one subject.

Otherwise, it's ready for resubmission. I'm sending it around again so that you can all "approve" the final version as submitted. Please send me your comments or approval by **June 30**. Thanks.

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Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Kennedy, Kathleen A
To: Wrage, Lisa Ann; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent
Date: Wednesday, June 19, 2013 3:09:09 PM

As I understand it, we have now verified that the infant previously coded (in error) as having severe ROP on the first ROP exam actually had no ROP. The changes I made to the numbers in the ROP secondary paper and figure were based on that. I think what's most important is that we report this accurately based on what we know now. It makes a big difference for the secondary paper because having one infant with severe ROP on the first exam was problematic (prompted a qualification in the recommendation that screening could safely begin at 31-32 weeks). If there was one infant reported differently/erroneously as having severe ROP in the SUPPORT manuscript, so be it. That difference would not change any of the study findings for the trial.

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 19, 2013 1:30 PM
To: Phelps, Dale; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Ok, I think this could be done as you describe, but I'll wait on Abhik because it is not consistent with the changes Kathleen proposes (taking this infant out of the severe ROP group and adding to the No ROP group).

I understand the question about optimizing Inositol data collection. I could ask Kris if the center could describe how the mistake on the SUPP10 form occurred (if they know) -- if that helps. I don't see why we should not ask that, but I'll wait on Abhik!

Thanks.
Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 19, 2013 2:23 PM
To: Wrage, Lisa Ann; Kathleen.A.Kennedy@uth.tmc.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

I believe that Abhik needs to guide us here. I need Abhik's permission to pursue this further. Clearly, if the GDB form is correct, the SUPPORT form is not (and vice versa).

I know we cannot change the locked SUPPORT database, and am not asking to do that. What I want is to optimize Inositol data collection, and to ensure that what we publish with Dr. Kennedy is not misleading.

What I think may be the solution for the paper Dr. Kennedy is preparing for publication is this:
This particular infant, in my opinion, will fall into the category of 'insufficient information to determine that age of onset of severe ROP". That would be because when we take into account

all the information we have (after we have it), the infant will not have a date of onset of severe ROP that meets our criteria for inclusion, and will therefore will fall out of the description/analysis of those that do have severe ROP (there are others also for other reasons). I have to study Fig. 1 again to be sure that really works.
I understand that Fig. 1 must remain consistent with the locked database.

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 19, 2013 10:53 AM
To: Phelps, Dale; Kathleen.A.Kennedy@uth.tmc.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Hi Dale,
The information I received was simply that the GDB was correct. There was no other information given. Let me know if you'd like me to forward these questions to Kris to ask the Center.
Thanks.
Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 19, 2013 1:47 PM
To: Wrage, Lisa Ann; Kathleen.A.Kennedy@uth.tmc.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thank you Lisa, Marie and Abhik,
This is extremely helpful. Please let the center know how much we appreciate their examination of the records.
We may need to ask for more information from them. It's ironic that it was a query from a manuscript reviewer that led to finding the error.

It is important for the iNOSITOL study to learn how or why the ROP data form for ROP outcomes had incorrect information entered in the now locked database. Since we are using almost the same version of that ROP dataform for Inositol, there is likely a design issue on the form or the sequence in filling it out or verifying it that makes it subject to such an error. There is still time for us to improve that full process for Inositol.

Did the center have any information on where or how the data entry discrepancy occurred ?
Was it a transcription error going from the medical records onto the SUPPORT data form for ROP outcomes? (or from GDB to SUPPORT)
Or was it a misunderstanding of the instructions for the dataform?
Or was it correct as recorded on the paper ROP dataform, but then there was a data entry error going from paper to the SUPPORT database?
We can work on a full "chain of events" listing to try to locate where in the chain for SUPPORT or for GDB there was a weakness, but this is a start. You and Kris or Marie may have information on other subjects where a query fixed similar problems, the 'near miss' phenomenon.

Understanding where in the sequence of recording the outcome that the discrepancy developed will help us reduce the chance of a similar occurrence using this form. Perhaps the form design needs more 'white space' to work in, or the MOP instructions are not clear (too long or too short or too complicated) or there needs to be more training/education on ROP, or anything else that we might discover. We will also work on additional internal recorded data cross checks that might have picked up the discrepancy and generated an earlier query.

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 19, 2013 7:10 AM
To: Kathleen.A.Kennedy@uth.tmc.edu; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: FW: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Good Morning,
The Center has replied that the NG03 for this infant is correct: No ROP.
Do you need other information?
Thanks.
Lisa

From: Wrage, Lisa Ann
Sent: Thursday, June 13, 2013 2:47 PM
To: 'Phelps, Dale'; Higgins, Rosemary (NIH/NICHD) [E]; 'Kathleen.A.Kennedy@uth.tmc.edu'
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Our query on this is in process, I'll let you know what we find out.
Thanks.
Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, June 13, 2013 10:10 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Kathleen.A.Kennedy@uth.tmc.edu'; Wrage, Lisa Ann
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Let's see what we learn, and then address this.
I understand the point you are making.
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 13, 2013 6:41 AM
To: Phelps, Dale; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'wrage@rti.org'
Cc: 'adas@rti.org'; 'mgantz@rti.org'
Subject: Re: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

The data need to be consistent with the original support report. Probably not worth much more

effort for one case.
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 12, 2013 06:14 PM
To: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Wrage, Lisa Ann <wrage@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik <adas@rti.org>; Gantz, Marie <mgantz@rti.org>
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thanks for brining to my attention Kathleen,
My last phrase was final, but should have had a period instead of 'and', thus ending;
Also, of course, the infant's GDB and SUPPORT paper research files.
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, June 12, 2013 2:54 PM
To: Phelps, Dale; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Dale, it looks like you might have intended to say something else when the last sentence ended.

I agree that this outcome (severe ROP in a 27 wk 1200g infant with no subsequent exams available) is highly improbable. I didn't think we needed the story for this manuscript but now I'm worried that it's an error because it's improbable and inconsistent with what's reported in the GDB for this baby. So I think we need to go to the source documents and try to get to the bottom of it before we publish that there was severe ROP on an initial exam at 33 weeks.

Lisa, the next steps would be figuring out what center and what Network number this is. Then we can go back to the coordinator to try to figure it out. If you need some help with this, please let me know.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, June 12, 2013 2:20 PM
To: Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Thank you very much Lisa,

1. The two figures came out very well without color. Nice work.

2. The clinical narrative for the infant "with severe ROP at first examination at 33 weeks PMA" provides very interesting data. It is a very low probability that this 27 week black female who was not SGA and had minimal complications in the hospital course ever had ROP at all.

The GDB data says she did have an examination and that there was no ROP.

Therefore I strongly suspect that the coding on the ROP data-form for SUPPORT was an error.

This must be queried.

Can we get paper copies of the ROP exam from the medical record? (HIPAA identifiers blocked out, but Network ID added). Time to go to the source data.

Also, of course, the infant's GDB and SUPPORT paper research files and

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, June 12, 2013 11:06 AM
To: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

Hi, I've attached the updated paper with responses in comments. Dale, I put a short clinical narrative for the baby with severe ROP at first ROP exam in a comment as well. I've also attached updated figures (the colored figures re-done in black/grey/white), Kathleen let me know what you think. I was skeptical about Figure 4 looking ok without color, but to me it appears doable. I should be able to pretty easily change these shades or line styles, if you prefer.

Thanks.

Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Monday, June 10, 2013 6:45 PM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu
Cc: Archer, Stephanie
Subject: RE: PEDIATRICS: Decision Letter for MS ID 2013-0900 - resent

I resent this because I previously sent a version of the document that still had old comments. You can ignore those and use this version.

I've made the suggested changes and reformatted this for Journal of Perinatology. The most recent set of changes are in orange text. There are a couple more questions for **Lisa**. If Lisa can easily find the clinical information about the one infant who had severe ROP on the first exam, that would be great (interesting) but I'm not sure we need it for the resubmission. I had to shorten the abstract. They give a page limit (20 including tables and references) for the manuscript instead of a word limit. We're way over, partly because we have 5 pages of acknowledgments and also because each table was supposed to be on a separate page. I hate to take anything out until we figure out what they really want.

Stephanie, the author instructions say that we need to justify having more than 6 authors. I assume that this goes in the cover letter. Do you have any language that we've used successfully for this in the past?

This journal charges ~$1200 for a color figure. That seems ridiculous to me. I thought the $150 per

figure in Pediatrics was bad enough. **Lisa**, can you try again to see if we can get the figures into black and white? I think Figure 2 could be done with shades of gray instead of blue. I'm hoping that figure 4 can be done with different kinds of dashed and dotted lines.

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Houston, TX 77030
713 500-6708

Blansfield, Earl (NIH/NICHD) [E]

From: Drazen, M.D., Jeff <jdrazen@nejm.org>
Sent: Thursday, June 20, 2013 11:30 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Please call me when you have a minute-617-930-5594

Jeffrey M. Drazen, M.D.
Editor-in-Chief, New England Journal of Medicine
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From: Luc Brion
To: Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: *Sent on Behalf of William E. Truog*
Date: Tuesday, June 18, 2013 3:32:03 PM

Barbara and Rose:

Once I have all the feedback and OK from the co-authors does the manuscript need to be resubmitted for additional review to the GDB committee and/or publication committee?

Luc

Luc P. Brion, MD
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Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
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5323 Harry Hines Boulevard, STOP 9063
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luc.brion@utsouthwestern.edu

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Tuesday, June 18, 2013 2:31 PM
To: Luc Brion
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: *Sent on Behalf of William E. Truog*

assume you would include a list

central line bundles
fluconazole prophylaxis
etc

That said-- could write a second brief report about other practice changes that may have influenced outcomes-- not directly related to the SUPPORT trial

THANKS**Luc Brion <Luc.Brion@utsouthwestern.edu> writes:**
Barbara;
Thanks for your prompt response.

About infection prophylaxis:

Reviewer #1 asked the following question:

"Were there separate initiatives in participating NRN centers to reduce nosocomial infection?"

We could further develop this.

Luc

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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Tuesday, June 18, 2013 2:23 PM
To: Luc Brion
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: *Sent on Behalf of William E. Truog*

L

Two pending discussions must take place before going forward with this manuscript:

Please answer yes or no to the following questions:

1. ***Should we initiate the planned survey before submitting to Pediatrics?***

Yes_____ No ____X___

If yes: should we add the two additional questions (thermoregulation in the DR and nosocomial infection prophylaxis) cLARIFY WHAT YOU MEAN BY INFECTION PROPHYLAXIS
WOULD CERTAINLY ADD TO THE SURVEY IF WE DECIDE TO SEND OUT-- NOW OR LATER

Yes_____ No_____

FYI, I attach the survey that was planned in the protocol.

I tentatively added the two additional processes of care one reviewer suggested to insert; I submit these two additional questions would be posthoc and subject to the same criticism raised by other reviewers. Personally I would use the survey as planned

We could to the survey in a relatively short time.

2. ***Should we compare with another network (VON, Canadian Network) before submitting to Pediatrics?***

Yes_____ No_____

Comparing with another network could take 6-24 months.

Based on your responses we could consider a conference call.

Thanks for your help and collaboration and best regards.

Luc

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luc.brion@utsouthwestern.edu

From: Mcbrien, James, D [mailto:jdmcbrien@cmh.edu]
Sent: Monday, June 17, 2013 9:25 AM
To: Luc Brion
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Stephanie Archer; Truog, William (MD)
Subject: *Sent on Behalf of William E. Truog*

Good morning Dr. Brion,

Please find attached three (3) de-identified reviews of your manuscript entitled "Changes in Therapy and Outcomes Associated with the SUPPORT Trial." Another review will hopefully be forthcoming.

Thanks,

Jim

James McBrien

Administrative Assistant III

Children's Mercy Hospitals and Clinics

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UT Southwestern Medical Center
The future of medicine, today.

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Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair
Department of Pediatrics, Emory University School of Medicine
President and CEO, Emory-Children's Center
SVP and Chief Academic Officer, Children's Healthcare of Atlanta
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From: Finer, Neil
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT NEJM responses to letters to the editors
Date: Saturday, June 15, 2013 10:47:55 PM
Attachments: SUPPORT NEJM Letter 1 Rev nf.doc
SUPPORT NEJM Letter 2 Ver rev NF.doc

Hi Wally
I have been on a plane = sorry to be delayed
I will be flying again in the morning but will look at whatever you do by tomorrow evening
Nice response
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, June 14, 2013 1:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: SUPPORT NEJM responses to letters to the editors

Hi Rose and Neil:

Enclosed is the first draft of the letter. I did not have Becky here to help so it took me longer than expected to get the first draft.

I still want to read several papers, go over, my notes and emails, and polish it but here are drafts so you can see where I am.

We still have plenty of time as the responses are not due until June 25th. I will work more on them on Monday and try to get them out to the group promptly after that.

Have a nice weekend.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
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Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

The oxygen saturation target part of the SUPPORT study was designed to test an oxygen saturation target in the lower range (85-89%) of recommended practice. The usual practice had been to target oxygen saturations ≥90%[1], and the median achieved oxygen saturations in a US multicenter study ranged from 92-98%.[2] Lower rates of retinopathy of prematurity without an increase in mortality were reported in several observational or retrospective studies of lower oxygen saturation targets, including one study that reported that infants managed with oxygen saturation targets 70-90% had a lower rate of retinopathy (6% versus 20%) and blindness (0% versus 6%) compared to infants managed with targets of 88-98%.[2] There was no effect on mortality or cerebral palsy at one year after birth.[2] Furthermore, targeting oxygen saturation of 70-90% was associated with over a 50% reduction in postnatal growth retardation rate, days ventilated, and days with supplemental oxygen.[3]

Because of the potential benefits of oxygen saturation targets below 90% without adverse effects apparent at the time, randomized controlled trials were conducted worldwide[4] to test the lower oxygen saturations targets versus the usual practice. Four of the five trials specified that the intervention group was the lower oxygen saturation target group and the fifth trial did not specify the intervention group. Thus, while language in the consent forms mentioned the high risk for retinopathy for all infants enrolled, language in the risks section did not mention an increased risk for retinopathy of prematurity as the purpose of the trial was to reduce achieved oxygen saturations which can be expected to reduce retinopathy. It is also important to note that while the SUPPORT trial compared targeting 85-89% versus 91-95% SpO2, the actual alarm limits were identical for both groups, and identical to the alarm limits used prior to the trial.

The use of death in the primary outcome of a trial is common and essential in many trials that enroll populations at risk of dying as death is a more important outcome than almost any other outcome. Indeed, most of the major National Institutes of Health Neonatal Research Network trials focused on the extremely preterm infants have death as part of the primary outcome measure independent of whether an increased risk for death was reasonably foreseeable. None of the studies of oxygen saturation targets in preterm infants published before the SUPPORT trial was designed had reported an increase in mortality, and thus, it was not reasonably foreseeable that mortality would be an increased risk. Based on the current medical literature, death was not listed as a potential risk of the lower oxygen saturation target allocation.

Finally, review of the evidence and reasonable understanding of the issues of the SUPPORT study have led a prominent group of scholars and leaders in bioethics and regulatory issues in pediatrics and human subject research to urge the Office of Human Research Protection (OHRP) to withdraw its initial conclusions.[5] OHRP has now clarified that they never questioned whether the design of the SUPPORT study was ethical and has put on hold all compliance actions. After a detailed review of the SUPPORT protocol, relevant consents, and literature, the National Institute of Health senior leadership stated that "...we respectfully disagree with the conclusions of OHRP...".

References:

1 Ellsbury DL, Acarregui MJ, McGuinness GA, Klein JM. Variability in the use of supplemental oxygen for bronchopulmonary dysplasia. J Pediatr 2002;140:247-9.
2. Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in finfants born less than 28 weeks gestation: the AVIOx study. Pediatrics 2006;188:1574.
3. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-10.
4. Askie LM, Brocklehurst P, Darlow BA, et al. NeOProM: neonatal oxygenation prospective meta-analysis collaboration study protocol. BMC Pediatr 2011;11:6.
5. Wilfond BS, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. N Engl J Med 2013;Jun 5.

As addressed in the letter by Dr. Tarnow-Mordi, Magnus and Caplan[1] stated that there is cause for concern in the initial decision by the Office for Human Research Protection (OHRP) to issue a letter of determination related to the SUPPORT study.[2] Magnus and Caplan conclude that such a determination by OHRP poses risk to research. OHRP has now corrected their initial assessment and put on hold all related compliance actions.

The SUPPORT study was approved by 23 institutional review boards in the US. Trials with similar design and consent forms were approved at multiple other institutions in the United States, United Kingdom, Canada, Australia, Germany, Israel, Finland, Argentina, and New Zealand.[3] Many of the respective institutional review boards and ethics committees had non-healthcare stakeholders including patients and patient advocates as now proposed in the 2010 Patient Protective Affordable Care Act that authorized the creation of the Patient-Centered Outcomes Research Institute (PCORI).[4] Patient- and family-centered care has been practiced for a long time in neonatology,[5] and research designs have been influenced by their approach for care for these vulnerable infants and their parents. The SUPPORT study was designed to reduce the risk of retinopathy of prematurity based on the then current literature that indicated that lower saturation targets reduced retinopathy and other adverse neonatal outcomes without an effect on mortality or developmental outcome.

Going forward, PCORI leaders have stated that they will provide guidance for involvement of patients, caregivers, clinicians, researchers, industry representatives, and the broader health care community in all phases of research.[4] PCORI is conducting roundtable discussions with these stakeholders to explore research perceptions and develop a deeper understanding of outcomes valued.[4] PCORI has been developing guidance for a year, and we look forward to the results of these discussions to improve neonatal care and specifically for comparative effectiveness studies such as SUPPORT. research. .

Comment [NF1]:

References:

1. Magnus D, Caplan, AL. Risk, Consent and SUPPORT. N Engl J Med. 2013;368:1864-5.
2. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-69.
3. Askie LM, Brocklehurst P, Darlow BA, et al. NeOProM: Neonatal oxygenation prospective meta-analysis collaboration study protocol. BMC Pediatr 2011;11:6.
4. Washington AE, Lipstein SH. The patient-centered outcomes research institute – promoting better information, decisions, and health. N Engl J Med 2011;365:e31.
5. Moore KA, Coker K, DuBuisson AB, Swett B, Edwards WH. Implementing potentially better practices for improving family-centered care in neonatal intensive care units: successes and challenges. Pediatrics 2003;111:e450-60.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Luc Brion
Cc: Pablo Sanchez; Wrage, Lisa Ann; doctorlevan@gmail.com
Subject: Re: Clearance | Levan, Changes in Therapy Associated with the SUPPORT Trial
Date: Saturday, June 15, 2013 5:32:03 AM

Yes
Ask bill

Sent from my iPhone

On Jun 14, 2013, at 11:32 PM, "Luc Brion" <Luc.Brion@UTSouthwestern.edu> wrote:

> No, I submitted to the protocol committee but I have not received any comments.
> Should I wait for an email from Bill Truog?
> Luc
>
> Luc P. Brion, MD
> Professor of Pediatrics
> Director, Fellowship Training Program in Neonatal-Perinatal Medicine
> The University of Texas Southwestern Medical Center at Dallas
> 5323 Harry Hines Boulevard, STOP 9063
> Dallas, TX 75390-9063
> Office: (214) 648-3903
> Fax: (214) 648-2481
> luc.brion@utsouthwestern.edu
> ++++++CONFIDENTIALITY NOTICE++++++
> All information included in this Communication, including attachments, is strictly confidential and intended solely for use by the addressee(s) identified above, and may contain privileged, confidential, proprietary and/or trade secret information entitled to protection and/or exempt from disclosure under applicable law. If you are not the intended recipient, please take notice that any use, distribution, or copying of this Communication is unauthorized and may be unlawful. If you have received this Communication in error, please notify the sender and delete this Communication from your computer. Please note that any views or opinions presented in this email are solely those of the author and do not necessarily represent those of UT Southwestern, University of Texas Southwestern Medical Center 5323 Harry Hines Blvd., Dallas TX 75390 www.utsouthwestern.edu (http://www.utsouthwestern.edu/)
>
>
> -----Original Message-----
> From: Pablo Sanchez
> Sent: Friday, June 14, 2013 10:31 PM
> To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
> Cc: (b)(6) @gmail.com
> Subject: RE: Clearance | Levan, Changes in Therapy Associated with the SUPPORT Trial
>
> Luc--have you received comments from internal reviewers? After you receive them, and incorporate them, then submit --if major changes, then re-consult those who worked on the paper--but NICHD is OK with the current version--the format for the letter is on the Pediatrics web site--pablo
>
> -----Original Message-----
> From: Luc Brion
> Sent: Friday, June 14, 2013 10:26 PM
> To: Pablo Sanchez; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
> Cc: (b)(6) @gmail.com
> Subject: FW: Clearance | Levan, Changes in Therapy Associated with the SUPPORT Trial

>
> Does this mean I may now submit to Pediatrics?
> Is there any template/format to submit for the letter to the editor?
> Luc
>
> Luc P. Brion, MD
> Professor of Pediatrics
> Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern Medical Center at Dallas
> 5323 Harry Hines Boulevard, STOP 9063
> Dallas, TX 75390-9063
> Office: (214) 648-3903
> Fax: (214) 648-2481
> luc.brion@utsouthwestern.edu
> ++++++CONFIDENTIALITY NOTICE++++++
> All information included in this Communication, including attachments, is strictly confidential and intended solely for use by the addressee(s) identified above, and may contain privileged, confidential, proprietary and/or trade secret information entitled to protection and/or exempt from disclosure under applicable law. If you are not the intended recipient, please take notice that any use, distribution, or copying of this Communication is unauthorized and may be unlawful. If you have received this Communication in error, please notify the sender and delete this Communication from your computer. Please note that any views or opinions presented in this email are solely those of the author and do not necessarily represent those of UT Southwestern. University of Texas Southwestern Medical Center 5323 Harry Hines Blvd., Dallas TX 75390 www.utsouthwestern.edu (http://www.utsouthwestern.edu/)
>
> -----Original Message-----
> From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
> Sent: Thursday, June 13, 2013 7:57 AM
> To: Luc Brion
> Subject: Clearance | Levan, Changes in Therapy Associated with the SUPPORT Trial
>
> NICHD has cleared Jackie's paper for submission, following the Publications reviews.
>
> Stephanie
> _____
> Stephanie Wilson Archer
> The Eunice Kennedy Shriver National Institute of Child Health and Human Development Pregnancy & Perinatology Branch
> 6100 Executive Boulevard, Room 4B03
> Rockville, MD 20852
>
> Tel. 301-496-0430
> Fax 301-496-3790
> archerst@mail.nih.gov
>
>
> -----Original Message-----
> From: NICHDWorkflow
> Sent: Wednesday, June 12, 2013 10:58 PM
> To: Archer, Stephanie (NIH/NICHD) [E]
> Cc: NICHDWorkflow
> Subject: Clearance Tracking: Journal Article/Scientific Manuscript Clearance Request Approved
>
> The following request for clearance was approved:
>
> Request ID: 11812
> Request Type: Journal Article/Scientific Manuscript

> Title: Changes in Therapy Associated with the SUPPORT Trial
> Requestor: NIH\archerst
> Branch/Center/Division: PPB/DER
> Status: Approved
>
> You may access the system at: http://insider.nichd.nih.gov/clearancetracking
>
>
>
> _____
>
> UT Southwestern Medical Center
> The future of medicine, today.
>
>

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"
Subject: SUPPORT NEJM responses to letters to the editors
Date: Friday, June 14, 2013 4:55:05 PM
Attachments: SUPPORT NEJM 2 Letters to the Editor.pdf
SUPPORT NEJM Letter 1 Ver 1.0.doc
SUPPORT NEJM Letter 2 Ver 1.0.doc

Hi Rose and Neil:

Enclosed is the first draft of the letter. I did not have Becky here to help so it took me longer than expected to get the first draft.

I still want to read several papers, go over, my notes and emails, and polish it but here are drafts so you can see where I am.

We still have plenty of time as the responses are not due until June 25th. I will work more on them on Monday and try to get them out to the group promptly after that.

Have a nice weekend.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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1700 6th Avenue South
176F Suite 9380R
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Cell: (b)(6)

Date Submitted: 24-May-2013
Ms. Number: 13-06780

Corr Au: Dr. William Tarnow-Mordi
University of Sydney
Hospital
Hawkesbury Road
Sydney, New South Wales 2145
Australia
E-Mail: williamtm@med.usyd.edu.au
Publish? Yes

Articles Referenced: May 16, 2013: Risk, Consent, and SUPPORT

To the Editor:

Magnus and Caplan(1) rightly conclude that criticisms of consent processes by the Office of Human Research Protections pose substantial risk to comparative effectiveness research, in all specialties. Looking forward, recommendations by US,(2, 3) UK(3) and Australian government agencies, some as recent as 2010, (2) provide a strategy to address this risk, by engaging consumers as partners throughout the research process. This includes engagement in prioritizing and designing studies, trial conduct, preparing study information, recruitment and interpreting and disseminating results. Outside the UK,(4) few trials in any field have yet realized this goal. Achieving it requires appropriate resources to train and support consumers as effective research partners.

Consumers can also be effective advocates. After her newborn daughter died at home from undiagnosed heart disease, one of us successfully lobbied Indiana to mandate pulse oximetry screening for congenital heart disease in all newborns. (5) This is now US federal policy. Consumer advocates could help broaden public support and participation in clinical research, to avert the threat of a significant slowdown in improvements in clinical care and survival.(1)

William Tarnow-Mordi,
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Melinda Cruz,
B. Sc.

Miracle Babies Foundation (Registered Charity),
Unit 6, 21 Governor Macquarie Drive
Chipping Norton, NSW 2170, Australia

Kristine Brite McCormick

Cora's Story, Inc. (Not for profit)
Indianapolis, Indiana, ~~United States~~

~~Tarnow-Mordi, William; Brite McCormick, Kristine; Cruz, Melinda~~
~~University of Sydney, , Cora's Story, Miracle Babies Foundation~~

~~**Disclosure:** None~~No potential conflict of interest relevant to this letter was reported.

1. Magnus D, Caplan AL. Risk, consent, and SUPPORT. N Engl J Med. 2013 May16; 368(20):1864-5
2. Washington AE, Lipstein SH. The Patient-Centered Outcomes Research Institute--promoting better information, decisions, and health. N Engl J Med. 2011 Oct 13;365(15):e31.
3. Tarnow-Mordi WO, Cruz M, Wilkinson D. Evaluating therapeutic hypothermia: parental perspectives should be explicitly represented in future research. Arch Pediatr Adolesc Med. 2012 Jun 1;166(6):578-9.
4. Stewart D, Wilson R, Selby P, Darbyshire J. Patient and public involvement. Ann Oncol. 2011 Nov;22 Suppl 7:vii54-vii56.
5. McCormick KB. Pulse oximetry advocacy. http://pulseoxadvocacy.com/ accessed 19 May 2013.

Date Submitted: 24 Apr 2013
Ms. Number: 13-05412

Corr Au: Prof. Leonard Glantz
Boston University
Albany Street
Talbot Building
Boston, Massachusetts 02118
United States
E-Mail: lglantz@bu.edu
Publish? Yes

Articles Referenced: Online Articles: Risk, Consent and the SUPPORT Study

To the Editor:
The central defense of the ethics of the SUPPORT trial is that the subjects were not put at increased risk of harm because they were randomized into two groups which both provided the â€œstandard of care.â€ â€”If the babies could not be harmed by randomization it would be equally true that they could not benefit. However, the consent formâ€™s benefit section states â€œIt is possible that that using lowered pulse oximeter ranges will result in fewer babies with severe retinopathy (ROP)â€ â€”There is no equivalent language that babies in the higher oxygenation arm might â€œpossiblyâ€ suffer more retinopathy. Nor is there any language that suggests the â€œpossibilityâ€ that lower levels of oxygenation could lead to an increase in deaths. This is especially troubling given the investigatorâ€™s statement that â€œDeath was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.â€ â€”The fact that â€œdeath competes with retinopathyâ€ underscores the need for language in the consent form to counterbalance the optimistic language in the benefits section.

Leonard H. Glantz, J.D.
Michael A. Grodin, M.D.

Both at
Boston University School of Public Health
Boston, MA
lglantz@bu.edu
Glantz, Leonard H.; Grodin, Michael
Boston University, Boston University School of Medicine

Disclosure: NoneNo potential conflict of interest relevant to this letter was reported.

1. Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely preterm infants. N Engl J Med 2013. DOI: 10.1056/ NEJMc130482

The oxygen saturation target part of the SUPPORT study was designed to test an oxygen saturation target in the lower range (85-89%) of recommended practice. The usual practice had been to target oxygen saturations ≥90%[1], and the median achieved oxygen saturations in a US multicenter study ranged from 92-98%.[2] Lower rates of retinopathy of prematurity without an increase in mortality were reported in several observational or retrospective studies of lower oxygen saturation targets, including one study that reported that infants managed with oxygen saturation targets 70-90% had a lower rate of retinopathy (6% versus 20%) and blindness (0% versus 6%) compared to infants managed with targets of 88-98%.[2] There was no effect on mortality or cerebral palsy at one year after birth.[2] Furthermore, targeting oxygen saturation of 70-90% was associated with over a 50% reduction in postnatal growth retardation rate, days ventilated, and days with supplemental oxygen.[3]

Because of the potential benefits of oxygen saturation targets below 90% without adverse effects apparent at the time, randomized controlled trials were conducted worldwide[4] to test the lower oxygen saturations targets versus the usual practice. Four of the five trials specified that the intervention group was the lower oxygen saturation target group and the fifth trial did not specify the intervention group. Thus, while language in the consent forms mentioned the high risk for retinopathy for all infants enrolled, language in the risks section did not mention an increased risk for retinopathy of prematurity as the purpose of the trial was to reduce achieved oxygen saturations which can be expected to reduce retinopathy.

The use of death in the primary outcome of a trial is common and essential in many trials that enroll populations at risk of dying as death is a more important outcome than almost any other outcome. Indeed, most of the major National Institutes of Health Neonatal Research Network trials focused on the extremely preterm infants have death as part of the primary outcome measure independent of whether an increased risk for death was reasonably foreseeable. None of the studies of oxygen saturation targets in preterm infants had reported an increase in mortality, and thus, it was not reasonably foreseeable that mortality would be an increased risk. Based on the current medical literature, death was not listed as a potential risk of the lower oxygen saturation target allocation.

Finally, review of the evidence and reasonable understanding of the issues of the SUPPORT study have led a prominent group of scholars and leaders in bioethics and regulatory issues in pediatrics and human subject research to urge the Office of Human Research Protection (OHRP) to withdraw its initial conclusions.[5] OHRP has now clarified that they never questioned whether the design of the SUPPORT study was ethical and has put on hold all compliance actions. After a detailed review of the SUPPORT protocol, relevant consents, and literature, the National Institute of Health senior leadership stated that "...we respectfully disagree with the conclusions of OHRP...".

References:

1 Ellsbury DL, Acarregui MJ, McGuinness GA, Klein JM. Variability in the use of supplemental oxygen for bronchopulmonary dysplasia. J Pediatr 2002;140:247-9.

2. Hagadorn JI, Furey AM, Nghiem TH, et al. Achieved versus intended pulse oximeter saturation in finfants born less than 28 weeks gestation: the AVIOx study. Pediatrics 2006;188:1574.
3. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-10.
4. Askie LM, Brocklehurst P, Darlow BA, et al. NeOProM: neonatal oxygenation prospective meta-analysis collaboration study protocol. BMC Pediatr 2011;11:6.
5. Wilfond BS, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. N Engl J Med 2013;Jun 5.

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Going forward, PCORI leaders have stated that they will provide guidance for involvement of patients, caregivers, clinicians, researchers, industry representatives, and the broader health care community in all phases of research.[4] PCORI is conducting roundtable discussions with these stakeholders to explore research perceptions and develop a deeper understanding of outcomes valued.[4] PCORI has been developing guidance for a year, and we look forward to the results of these discussions to improve neonatal care and research.

References:

1. Magnus D, Caplan, AL. Risk, Consent and SUPPORT. N Engl J Med. 2013;368:1864-5.
2. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-69.
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5. Moore KA, Coker K, DuBuisson AB, Swett B, Edwards WH. Implementing potentially better practices for improving family-centered care in neonatal intensive care units: successes and challenges. Pediatrics 2003;111:e450-60.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Wally Carlo, M.D.
Cc: nfiner@ucsd.edu
Subject: Re: SUPPORT NEJM responses to letters to the editors
Date: Friday, June 14, 2013 6:10:49 PM

Wally and Neil
I do not need to be an author
Thanks
Rose

Sent from my iPhone

On Jun 14, 2013, at 4:55 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> Hi Rose and Neil:
>
> Enclosed is the first draft of the letter. I did not have Becky here to help so it took me longer than expected to get the first draft.
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> I still want to read several papers, go over, my notes and emails, and polish it but here are drafts so you can see where I am.
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> We still have plenty of time as the responses are not due until June 25th. I will work more on them on Monday and try to get them out to the group promptly after that.
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> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 1700 6th Avenue South
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> Cell (b)(6)
>
> <SUPPORT NEJM 2 Letters to the Editor.pdf>
>
> <SUPPORT NEJM Letter 1 Ver 1.0.doc>
>
> <SUPPORT NEJM Letter 2 Ver 1.0.doc>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: McGarey, Barbara (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]
Subject: RE: (b)(5) (b)(5)
Date: Friday, June 14, 2013 4:00:00 PM
Attachments: NRN Policies and procedures.pdf

Hi
Here are the NRN policies and procedures
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: McGarey, Barbara (NIH/OD) [E]
Sent: Wednesday, June 12, 2013 11:38 AM
To: Bonham, Valerie (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: (b)(5) (b)(5)

Hi Val, Dr. Higgins is requesting (b)(5) that I think you are best positioned to answer going forward. I'll drop by and brief you on it. Julie is aware you'll be handling so just coordinate as needed if (b)(5)

Thanks,

Barb

Barbara M. McGarey, J.D.
Deputy Associate General Counsel for Public Health, NIH
Office of the General Counsel, PHD, NIH Branch
31 Center Drive, Rm 2B-50
Bethesda, MD 20892-2111
(301) 496-6043 (phone)
(301) 402-1034 (fax)
mcgareyb@od.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, June 11, 2013 5:13 PM
To: McGarey, Barbara (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: FW: (b)(5)

(b)(5)

(b)(5) Let me know what you think.

Thanks for your help.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:03 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: (b)(5)

(b)(5)

Hi

(b)(5)

(b)(5)

Let me know if there are questions.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

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6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 7:41 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: (b)(5)
(b)(5)

More on the most recent info request, which did not come to us, of course (we were only cc:ed), but only to the investigators and RTI...

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, June 09, 2013 10:16 PM
To: Muroff, Julie (NIH/OD) [E]
Cc: McGarey, Barbara (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]
Subject: Re: (b)(5)
(b)(5)

Thank you so much Julie. (b)(5)
(b)(5) I guess that is why our jobs are quietly entertaining.

I am sharing via cc your opinion with pat white and Alan Guttmacher. (For reasons I do not understand my iPhone thinks Alan should be with caps but not pat.).

Alan - we look forward to response from nichd. pat, we look forward to an explanation of why your name is not capitalized.

Warmly,
Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH

301 496 1455
kathy.hudson@nih.gov

On Jun 9, 2013, at 7:51 PM, "Muroff, Julie (NIH/OD) [E]" <muroffj@od.nih.gov> wrote:

(b)(5)

We would be happy to elaborate by phone or meeting.

Julie A. Muroff, J.D., LL.M.
Senior Attorney
HHS Office of the General Counsel, PHD, NIH Branch
31 Center Drive, Bldg. 31, Rm.2B-47
Bethesda, MD 20892
301-451-4910 (direct)
301-402-1034 (Fax)
Julie_Muroff@nih.gov

From: McGarey, Barbara (NIH/OD) [E]
Sent: Friday, June 07, 2013 10:47 PM
To: Rockey, Sally (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: Re: (b)(5)

(b)(5)

We will take a look and advise.

From: Rockey, Sally (NIH/OD) [E]
Sent: Friday, June 07, 2013 09:58 PM
To: Hudson, Kathy (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: (b)(5)

(b)(5)

(b)(5)

Sally J. Rockey, Ph.D.
NIH Deputy Director for Extramural Research
OD/NIH/DHHS
One Center Drive
Building 1, Room 144
Bethesda, MD 20892
301-496-1096 (BLDG. 1)
301-435-2698 (ROCK I)
301-402-3469 Fax
rockeysa@od.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, June 07, 2013 9:29 PM
To: Rockey, Sally (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: (b)(5)
(b)(5)

I am thinking our policy (b)(5)
(b)(5)

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, June 07, 2013 5:19 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FW: (b)(5)
(b)(5)

FYI...

Alan

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: adas@rti.org; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.

Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

Policy and Procedures

NICHD Neonatal Research Network

Originally approved 3/3/1993;
Updated 3/1/2001; 4/2003; 3/2004; 2/2007; 2/2010; 1/2011

Table of Contents

Chapter

1

The NICHD Neonatal Research Network

1.1 Background

Modern neonatal medicine is a rapidly developing, highly technical environment in which principles of management and innovative methodologies change within months, before rigorously controlled studies of their safety and efficacy can be conducted. In November 1982, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal and Child Health Research Committee reviewed the need for better studies of the management of infants in neonatal intensive care units (NICU). The committee recommended that cooperative, multi-institutional studies be conducted by the medical community with the assistance of NICHD.

In response, the NICHD established a cooperative network of NICUs in 1986 to undertake multi-center clinical studies investigating the safety and efficacy of treatment and management strategies of newborns. By providing large populations through a network of centers using common protocols, questions could be answered more rapidly than by individual centers acting alone. The funding mechanisms are five-year, competitively awarded cooperative agreements that provided for scientific involvement of the NICHD staff to assist the scientific community in the development and implementation of protocols and in the analysis and dissemination of study results.

Originally named the Cooperative Multicenter Network of Neonatal Intensive Care Units, the initial NICHD Neonatal Research Network (NRN) was composed of seven participating university centers and a data center. The first protocol initiated by the Network was a large, randomized trial of intravenous gamma globulin (IVIG) to prevent sepsis in infants <1,500 grams. Since 1987, the Network has maintained a Generic Database (GDB) of information on preterm infants born in the NRN. The GDB collects observational baseline data on both mothers and infants, the therapies used, and outcomes of the infants. These data are used to: examine associations between baseline characteristics, treatments, and outcomes; track trends in incidences of disease and effectiveness of therapies; and identify questions requiring additional in-depth research.

As of the 2006-2011 cycle, the NRN comprises 16 academic institutions and a data coordinating center, and is involved in multiple ongoing clinical trials and observational studies of neonates. Appendix A contains a list of the current NRN member organizations. Details on current trials are available at www.clinicaltrials.gov and at the NRN website neonatal.rti.org.

1.2 Objective

As stated in the Request for Applications (RFA HD10-003):

> "The objective of this program is to facilitate the advancement of neonatal care by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, can study the required numbers of patients and can provide answers more rapidly that individual centers acting alone.
>
> The infrastructure is set up for the ideal randomized double-blinded placebo controlled trial with the ability to follow short term (clinical effect) and long term (neurodevelopmental outcome) measures. The infrastructure is also set up for observational, longitudinal studies in the neonatal intensive care unit setting. Many randomized clinical trials involve the need for baseline information regarding disease incidence and outcome, which is available from the generic database of neonates...in the current Neonatal Research Network. This initiative will foster conducting multicenter trials in the neonatal population."

1.3 Request for Applications Clinical Center Requirements

NRN applicants are required to demonstrate research productivity in clinical trials, an established neonatal follow-up clinic that successfully follows a majority of the institution's discharged high-risk infants, appropriate subspecialty involvement, and an operational system of data collection. The grantees agreed to provide data to the NRN Generic Database, to accept the coordinating role of the group and the cooperative nature of the Network, to participate in ongoing protocols, and to comply with capitation funding.

Specific eligibility criteria detailed in RFA HD-04-010 included:

- *Academic productivity*. A record of research productivity by the clinical center in previous or ongoing clinical trials, especially those of a cooperative or multicenter design, with contributions in research development and design, patient recruitment, retention and study completion, data collection and analysis, and a track record of publications
- *Neonatology staffing*. A level III/IV NICU that admits inborn and outborn infants with at least four board-certified, academically-oriented neonatologists on staff
- *Population available for clinical trials*. At least 500 neonatal admissions per year with no more than 30 percent outborn
- *Maternal-fetal medicine unit*. An established maternal-fetal medicine service for delivery of high-risk pregnancies with perinatologists active in clinical research and a history of collaboration between Neonatology and Perinatology towards excellent clinical care, database accessibility, and research productivity
- *Subspecialties*. Availability of subspecialists for examinations and procedures
- *Follow-up program*. An established neonatal follow-up program with a designated facility in place at the clinical center. The program must have experience in tracking and retaining patients

at 18-22 months corrected gestational age with at least an 80 percent follow up success rate; a follow up rate of 90% is highly desirable. Some protocols may require school age follow-up at 6-7.5 years of age

- *Perinatal data system*. An established electronic perinatal data system must be in place to collect and analyze patient information.
- *Research staff*. A full-time research nurse coordinator with additional research staff available, as needed, to cover patient recruitment on nights, weekends, and holidays.
- *Intent to participate*. A clearly expressed intent to participate in a cooperative manner with other NRN clinical centers, the NICHD, and the data coordinating center in all aspect of research as outlined in the RFA. NRN protocols must be given priority at awarded clinical sites. Sites are expected to participate in all trials, unless they described trials in their grant application that conflict with ongoing network trials. In addition, Steering Committee meetings are held in the Washington, DC metro area four times per year. The PI or his/her designee is required to attend the meetings in their entirety.
- *Departmental and institutional commitment*. The departmental and institution commits to participate in NRN research, including support for grants management, personnel management, space allocation, procurement, and equipment, as well as general support for research.
- *Acceptance of the budgetary mechanism*. The institution agrees to cooperate with the policy for capitation of research costs for each individual protocol. The appropriate Federal cost policies and regulations governing NIH grant programs are applied (see NIH Grants Policy Statement at grants.nih.gov/grants/policy for details).

The full RFA is available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-10-003.html.

1.4 Request for Applications Data Center Requirements

The NRN Data Coordinating Center (DCC) must cooperate with multiple sites involved in clinical trials in design, execution, data collection and data analysis resulting in publication for multicenter randomized and observational clinical trials, particularly in the area of neonatal-perinatal medicine.

Specific eligibility criteria detailed in RFA HD07-002 included:

- *Academic productivity*. DCC applicants must provide evidence of research productivity by the data coordinating center in previous or ongoing clinical trials, especially those of a cooperative or multicenter design in the field of neonatal-perinatal medicine. Contributions in key areas of research development and design, data collection and analysis, monitoring of trial progress, and track record of publications that resulted from participation in the studies should be listed.
- *Data and communications management*. DCC staff must have the ability to assist in protocol development with respect to design of manual of procedures, data collection forms, data collection systems, electronic technology, and data entry systems. Prior experience in data quality assurance is required, with experience in neonatal-perinatal medicine studies and Food and Drug Administration (FDA) Investigational New Drug protocols preferred. The DCC must

have knowledge of federal patient-privacy and data confidentiality requirements and appropriate experience in ensuring that relevant mechanisms and procedures are in place.

- *Reporting capabilities*. The DCC must generate monthly reports on subject enrollment for multiple concurrent studies, in addition to reports for use by the Data Safety Monitoring Committee (DSMC), NRN Advisory Board, and the Steering Committee, including documentation and dissemination of meeting and conference call minutes.
- *Logistical and other support services*. The DCC must provide logistical support for the NRN Steering Committee meetings (four per year in the DC metropolitan area) and conference calls, the Data Safety and Monitoring Committee meetings (one per year and as needed) and conference calls, and other meetings as needed by the NICHD NRN.
- *On- and off-site monitoring*. The DCC must organize and conduct on-site and off-site monitoring for clinical research studies. Generation of data errors and needed edits is required. The DCC needs to ensure that the NRN sites fully comply with NIH regulatory requirements, including human subject protections, informed consent, reporting of adverse events, human and animal safety and welfare provisions, and FDA requirements as indicated by specific studies.
- *Technology transfer, data management, and protocol training*. The DCC must assist the clinical sites in data management and communication activities. The DCC will arrange training sessions for scientific protocols, ongoing yearly certifications necessary for NRN studies (e.g., developmental tests, standardized physician examinations, follow up), and data entry, as needed.
- *Management and personnel.* DCC should have flexibility in staffing to be able to respond to the changing needs and seasonal variation in work effort of the NICHD NRN. The DCC must be able to estimate the appropriateness and reasonableness of resources needed for individual projects and manage those resources efficiently during the course of the research. Flexibility among personnel based on effort needed is required. Experience with subcontracts is required.
  - *Principal investigator.* The DCC must provide a senior principal investigator (PI) with clinical trials and statistical expertise and a doctoral degree in a relevant field, such as statistics, biostatistics, or epidemiology. The PI must have the skills, knowledge, and resources necessary in biostatistics, data management, data analysis, and project management to interact with the broad and diverse group of neonatal clinical investigators who are in the NICHD NRN. He or she is required to commit 100 percent of his/her effort to the DCC activities of the NICHD NRN.
  - *Research staff*. In addition to the PI, the DCC must provide: an alternate PI, statisticians, coordinators or research project assistants, programming and analytic staff (including supervisory staff and software expertise staff), data processing staff, and logistics and support staff.
- *Facilities.* The DCC must have an office in the Washington, DC metropolitan area, preferably in close proximity to NIH.

The full DCC RFA is available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-10-003.html.

Chapter

2

Roles and Responsibilities

This section details the roles and responsibilities of the NRN Clinical Centers, the Data Coordinating Center, and NICHD program staff.

2.1 Clinical Centers

2.1.1 Institutional Responsibilities

As described in Chapter 1, the clinical centers participating in the NICHD Neonatal Research Network represent academic institutions with experience in multicenter clinical research. They have agreed to abide by NRN study protocols and have comparable staff, facilities, and equipment.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development provides funding to each clinical center and the DCC through a National Institutes of Health (NIH) cooperative agreement (U10 award mechanisms). NIH uses this U10 assistance mechanism whenever it anticipates NIH scientific and/or programmatic staff having substantial involvement with the awardee during performance of the activity.

2.1.2 Resources

As part of this funding, NICHD provides a base award to each center to cover partial or full salaries for a principal investigator, a research coordinator, and data entry personnel. As per the RFA, clinical centers must provide:

- Principal Investigator (PI): 10 percent effort
- Alternate PI, Follow Up PI, additional investigator, or additional PI support: (as of 4/1/2011) up to 20 percent effort
- Research Coordinator: 100 percent effort
- Data Entry Clerk: 50 percent effort

Also as per the RFA, "Additional research staff should be available, as many protocols require patient recruitment at night and on weekends."

Finally, additional research expertise (research pharmacy staff, ophthalmologists, surgeons, etc.) may be required for implementation of specific protocols.

2.1.3 Staff Roles and Responsibilities

Principal Investigator
Each institution must designate a Principal Investigator (PI) responsible for all aspects of the center's participation in the Neonatal Research Network. The Principal Investigator participates, with the NICHD and Data Coordinating Center, as a member of the NRN Steering Committee.

The Principal Investigator has primary responsibility for:

- Identifying priority areas for research
- Developing and implementing the network protocols
- Collecting and transmitting the data to the data-coordinating center
- Analyzing the data and publishing results of the NRN trials

As such, the PI's oversight responsibilities include:

- Preparing the center's budget and annual progress report
- Obtaining and maintaining required Institutional Review Board (IRB) approvals, and ensuring that the necessary financial arrangements and federal assurances are in place before participation in each study
- Ensuring collection and transmission of accurate data to the DCC in a timely manner
- Participating in NRN quality assurance efforts, including cooperating during site visits, responding promptly to data center inquiries, etc.
- Hiring and supervising qualified study personnel
- Securing the cooperation of his/her institution and colleagues in NRN research efforts
- Communicating NRN activities and issues to their research staff in a timely fashion, particularly those issues likely to affect the day-to-day operations of ongoing or upcoming NRN protocols
- For sites that are also members of the NICHD Maternal-Fetal Medicine Unit (MFMU) Network, communicating with the MFMU PI, reviewing ongoing and planned research of the two Networks to alert staff to potential conflicts between protocols, identify areas of common interest and potential collaboration, and offer advice within the primary areas of expertise.
- Notifying the Data Coordinating Center and NICHD Program Scientist of any serious adverse events during conduct of NRN protocols
- Designating an alternate principal investigator to act as the clinical center PI whenever the principal investigator is not available. As acting, the alternate PI should have full authority to act in the PI's stead whenever the PI is unavailable, including attending required NRN meetings and/or teleconferences, voting on steering committee and sub-committee issues, and have full access to all NRN records.
- Notification to NICHD and the DCC of any staff changes in a timely manner

Research Coordinator
One research coordinator will be appointed at each Clinical Center to oversee the conduct of NRN clinical trials. Under the direction of the PI, the Research Coordinator is responsible for ensuring the

successful conduct and coordination of Network protocols. Research coordinators participate in NRN protocol development and implementation as members of protocol subcommittees.

In addition, Research Coordinators provide assistance during NRN site visits to their own institutions, and may also participate in site visits to other centers. Experienced NRN Research Coordinators may be asked to assist in mentoring new coordinators at new NRN sites, as needed.

Under the supervision of the PI, the research coordinator is responsible for:

- Assisting in the day-to-day operations of implementing network protocols, including adhering to protocols, collecting data, supervising data transmission, monitoring data quality, training staff, and procuring adequate equipment and supplies to support Network studies
- Maintaining routine data quality assurance methods for staff under his/her supervision
- Supervising data entry activities, including instructing and certifying data entry personnel in software and hardware usage, quality assurance of data entry, etc.
- Maintaining a central file of protocols, manuals, data forms, network correspondence, and performance reports
- Collaborating with the PIs and data center in developing protocols, manuals of operation, and data collection forms
- Attending at least two Steering Committee meetings per year, the monthly Coordinator conference call, and the meetings of any subcommittees of which they are a member

The supervisory duties should require no more than half time. The remainder of research coordinator efforts should be devoted to NRN subject recruitment and day-to-day site needs and administrative issues, including IRB protocol submissions and renewals, Steering Committee attendance (at least two meetings per year), site visits, training sessions, protocol development, participation in conference calls, etc., as well as center data collection as required.

Data Entry Clerk

Each clinical center will appoint a half-time data entry clerk. The data entry clerk is responsible for collecting completed data forms, entering data accurately into the NRN data entry system, and transmitting the entries to the DCC in a timely manner.

Additional research staff

Additional research staff should be available 24 hours a day and 7 days a week to cover protocol recruitment and/or implementation at night and on weekends and holidays. Additional research expertise (research pharmacy staff, ophthalmologists, etc.) may also be required for implementation of specific protocols.

2.2 Data Coordinating Center

2.2.1 Institutional Responsibilities

The NRN data coordinating center's primary objective is to provide statistical leadership in the design, execution, and analysis of medical investigations, insuring that the results of each study are of the highest scientific quality and meet rigorous biostatistical standards. The specific objectives of the NRN DCC are to provide biostatistical support and consultation in the areas of protocol design, execution, close-out, and analysis for the multi-institutional observational and experimental studies in the field of neonatology. The DCC cooperates effectively in all Network functions with NICHD and the clinical centers in administration and coordination of the protocols.

The data coordinating center will:

- Collaborate in the development, implementation, and monitoring of common Network protocols;
- Provide data management, including preparation of data and safety reports for the Data Monitoring Committee and preparation of data reports for Network subcommittees, centers, and public data files;
- Collaborate in the analysis of data and publication of results of the Neonatal Research Network trials and studies; and
- Provide the logistical support necessary to run an efficient and productive network.

In addition, the DCC collaborates with NIH to establish and refine organizational procedures to optimize the efficiency of the Network. The DCC may coordinate external services, including procuring study drugs, equipment, and other supplies, implementing masking methods, and executing subcontracts for diagnostic tests and consultancy agreements with outside experts. The DCC is responsible for distributing study documents, including protocols, manuals, data collection forms, and study technical memos, to the clinical centers.

2.2.2 Resources

As per the DCC RFA, the following categories of personnel are needed to insure excellence in the day-to-day activities of the DCC:

- Principal Investigator
- Alternate PI
- Statisticians
- Coordinators and/or Research Project Assistants
- Programming and analytic staff (including supervisory staff and software expertise)
- Data processing staff
- Logistics and support staff

The DCC should have some degree of flexibility in staffing to be able to respond to the changing needs and seasonal variation in work effort of the NICHD NRN.

The DCC staff is empowered to communicate directly with network investigators, research staff at each clinical center, NICHD, and members of the NRN subcommittees, as needed. The DCC principal investigator and staff collaborate with the NICHD Project Officer and staff in the overall administration, planning, and monitoring of NRN activities.

2.2.3 Staff Roles and Responsibilities

Principal Investigator
Similar to the clinical center PIs, the DCC Principal Investigator bears overall responsibility for the DCC's participation and performance in the Network. He or she is a full voting member of the NRN Steering Committee and is responsible for contributing to the development of new protocols, analyses, and publications, monitoring the conduct of Network studies, monitoring data collection, and ensuring adherence to quality assurance measures. He or she is responsible for ensuring that the necessary financial arrangements, IRB approvals, and federal assurances are in place before participation in each study, and for completing any reporting requirements.

As such, the DCC PI's responsibilities include:

- Preparing the DCC's budget and annual progress report
- Obtaining and maintaining required Institutional Review Board (IRB) approvals
- Supervising NRN quality assurance efforts, including conducting site visits, responding promptly to Steering Committee inquiries, etc.
- Hiring and supervising qualified study personnel
- Securing the cooperation of his/her institution and colleagues in NRN research efforts
- Designating an alternate principal investigator to act as the data coordinating center PI whenever the principal investigator is not available. As acting, the alternate PI should have full authority to act in the PI's stead whenever the PI is unavailable, including attending required NRN meetings and/or teleconferences, voting on steering committee and sub-committee issues, and have full access to all NRN records.

In addition to these duties, the DCC PI reports to the Steering Committee and serves as its administrative arm – implementing Steering Committee decisions regarding protocol execution, data processing, and analysis. The DCC PI collaborates closely with clinical center PIs and NICHD staff on biostatistical issues related to the design, implementation, conduct, and analysis of Network studies. He or she participates on or assists every established board and committee in the Network.

Per the DCC RFA and as detailed below, the DCC Principal Investigator has primary oversight responsibility for:

- Assistance with identification of priority areas for research
- Developing and implementing the network protocols
- Supervision and acquisition of the data to the data-coordinating center

- Data management and quality control monitoring
- Logistical support for the NRN
- Preparation of reports as needed
- Analysis of data and publication of results of the NRN trials

Assistance with identification of priority areas for research. The DCC PI and his/her staff collaborate with the Network in the development of study protocols, including developing patient eligibility criteria, randomization and/or stratification techniques, treatment and/or follow-up schedules, specification of primary and secondary outcomes and measures, sample size determination, statistical analysis plans, and a projected timetable of tasks to be conducted.

In addition, the DCC PI works with the NICHD Program Scientist, Steering Committee, and subcommittees to prioritize the NRN's statistical analytic needs with primary protocols given first priority.

Developing and implementing Network protocols. Before the initiation of a study, the DCC PI and his/her staff work with the study PI, protocol subcommittee, and research coordinators to finalize the protocol, and develop data collection forms and a detailed manual of operation. The data coordinating center assumes principal responsibility for the design of sampling and/or randomization procedures, and specification of the performance monitoring procedures.

For experimental studies that use coded medications (e.g., placebo-controlled), the DCC assists the pharmacies and/or packaging companies with the medication masking procedures.

For drug and device trials that may fall under the regulatory authority of the U.S. Food and Drug Administration (FDA), the DCC works with NICHD and the study PI to provide necessary data, documentation, and other required FDA correspondence and reporting for Investigation New Drug (IND) applications.

DCC staff review clinical center IRB consent forms to ensure compliance with Network requirements. If necessary, the DCC applies for a Certificate of Confidentiality on behalf of all of the Network centers.

The DCC works with the study PI to plan and conduct necessary training sessions on protocol implementation and data processing procedures.

Supervision and acquisition of the data to the data-coordinating center. The DCC serves as the central repository for clinical and laboratory data. It provides a computerized data management system that allows clinical center staff to enter and transmit data to the DCC, or enter data via the Internet. The data center provides ongoing training of study personnel on data processing procedures, as needed.

Data management and quality control monitoring. The DCC provides and maintains computerized data management systems. DCC staff monitors and reports on data quality, protocol adherence, and

recruitment status. It reviews eligibility and monitors enrollment of study patients, and participates in site visits. DCC staff assists in the coordination of and participates in site visits and data review visits, as required for quality assurance.

In addition, the DCC PI reports to the external Data Safety and Monitoring Committee (DSMC). The DCC PI notifies the chairperson of the DSMC, as needed, of any unexpected, serious, and protocol-related adverse events or apparent trends in data that patient safety. At periodic intervals, as specified in the protocols, the DCC PI provides the DSMC with confidential interim analyses of study data related to protocol performance, patient safety, and emerging results.

To ensure that patient data and outcomes are properly documented, once study recruitment and implementation have been completed, the DCC PI and his/her staff conduct a final check (i.e., data cleaning) of each study patient's data record and works with the clinical centers to resolve any outstanding missing or inconsistent data items. The DCC PI and his/her staff conduct statistical analyses of study results and assist investigators in the preparation of presentations and manuscripts for publication. DCC staff work with the study PI and protocol subcommittee, conducting statistical analyses of primary and secondary studies and reviewing abstracts, presentations, and/or manuscripts prior to publication. Study data reside centrally at the DCC, whose staff is responsible for complete documentation of the study and archival storage of the dataset.

Following publication, the DCC PI and his/her staff close-out the study, ensuring that all relevant study documents and data are organized and archived for future access. The data center sends a copy of the relevant study documentation to NICHD, including all revisions of the protocol, manual and forms (including study definitions), the data tables, and an electronic data file.

Logistical support for the NRN. As the administrative arm of the Steering Committee, the DCC is responsible for providing logistical and administrative support for Steering Committee and other meetings, teleconferences, and training sessions, including securing meeting facilities and equipment, and taking and distributing meeting minutes. It is also responsible for creating and maintaining records for all NRN protocols in the ClinicalTrials.gov database.

The DCC also maintains both the NRN's private and public websites. The public website includes general information about the NRN and its ongoing and completed studies. The private website includes study documents, a staff directory, Steering Committee and subcommittee meeting minutes, and other documents necessary to the efficient functioning of the Network.

The DCC produces a newsletter to Network staff on the latest developments in the NRN.

Preparation of reports as needed. The DCC PI is responsible for generating the following reports:

- Monthly subject enrollment reports for ongoing studies
- Clinical center "Network Snapshots"
- Appropriate reports for the DSMC
- Special reports as required by the Steering Committee, its subcommittees, and/or NICHD

Statisticians
DCC statisticians assist the Network PIs in designing study protocols, including determining sample size and developing statistical analysis plans. They work with the DCC PI to develop planned interim analyses for the DSMC on protocol performance, patient safety, and emerging results. DCC statisticians analyze study results and assist investigators in the preparation of presentations and manuscripts for publication of primary and secondary studies.

Coordinators and/or Research Project Assistants
DCC coordinators and research project assistants work closely with the DCC PI to implement Steering Committee decisions. They assist with obtaining and maintaining required IRB approvals, reviewing the clinical sites' IRB consent forms for compliance with Network requirements, gathering documentation for IND applications and applying for Certificates of Confidentiality. DCC Coordinators are the principal liaisons with the clinical research coordinators, working with them, the study PIs, and the DCC programming staff to finalize protocols and develop data collection forms and manuals of operation, and to plan and conduct necessary training sessions on protocol implementation and data processing procedures. DCC coordinators set up and participate in site and data review visits for quality assurance. In addition, they work with other DCC staff to maintain and update the NRN's private and public websites and to produce the NRN newsletter.

Programming, analytic, and data processing staff
DCC programming staff is primarily responsible for developing, maintaining, and updating the NRN data management systems. They work with the study PIs and DCC coordinators to develop protocol randomization methods (e.g., phone call-in systems), program the data entry system, manage data transmission, and provide support to the clinical sites to resolve any data entry and transmission issues. DCC programming staff works with the DCC PI and coordinators to monitor data quality and assist with data clean up prior to statistical analysis. In addition, programming staff assist the DCC PI to generate required NRN reports.

Logistics and support staff
DCC support staff is responsible for providing logistical support for the NRN – scheduling meetings and teleconferences, securing meeting and lodging facilities and equipment, taking and distributing meeting minutes, etc.

2.3 NICHD Staff

2.3.1 Institutional Responsibilities

NICHD developed the cooperative agreement (U10) in an ongoing multicenter clinical program designed to investigate the safety and efficacy of treatment and management strategies to care for newborn infants, especially those related to the management of low birth weight infants. The goal of the program is to facilitate evaluation of strategies to improve the outcome of infants by establishing a network of academic centers that can study ample numbers of patients to provide evidence to promote and improve the practice of clinical neonatology.

2.3.2 Resources

NICHD provides the following staff to ensure scientific and programmatic stewardship of the award:

- NICHD Program Officer
- NICHD Program Scientist
- Network Coordinator
- Grants Management Officer
- Grants Management Specialist

2.3.3 Staff Roles and Responsibilities

NICHD Project Officer
A NIH program officer is responsible for the traditional program management and stewardship of the NRN. As stated in the RFAs, the NRN Project Officer is responsible for review and oversight of the cooperative agreement, including:

- "Carry out continuous review of all activities to ensure that the objectives are being met and that all regulatory, fiscal, and administrative matters are handled according to NIH guidelines.
- Have the option to withhold support to a participating institution if technical performance requirements are not met.
- Perform other duties required for normal program stewardship of grants.
- Assurance of the scientific merit of the trials, including the option to withhold support of a participating center if technical performance requirements such as protocol compliance, enrollment targets, or randomization of subjects are not met.
- Initiation of a decision to modify or terminate a study based on the advice of the data center, Data Safety and Monitoring Committee, and/or Advisory Board with the mutual consent of the Steering Committee."

NICHD Program Scientist
The NICHD Neonatal Research Network Program Scientist – a neonatologist within NICHD's Perinatology and Pregnancy Branch – provides substantial scientific involvement as a participant in the scientific efforts of the Network, as well as in review and oversight of the efforts of the Network.

The NICHD Program Scientist is responsible for policy development, implementation, and conduct, budget formulation, resource allocation, and identification of new areas of research. He or she monitors and ensures the effective execution of the program on a day-to-day basis, evaluating the quality and effectiveness, as well as the scientific merit and potential impact, of the program. He or she is a voting member of the NRN Steering Committee, and an active member of all standing committees, protocol subcommittees, and working groups of the Network.

As per the RFAs, the NICHD Program Scientist is responsible for:

- Assisting in the identification of important areas of study
- Assisting in the development of study protocols
- Assisting in the development and review of capitation-based budgets, including the identification of study costs and special institutional needs
- Assisting in the review and evaluation of each stage of the program before subsequent stages are started, in conjunction with the Steering Committee and the Advisory Board
- Assisting in the conduct of the trials, including ongoing review of progress, possible redirection of activities to improve performance and cooperation, and frequent communication with other members of the Steering Committee
- Assisting in reporting results to the community of investigators and health care recipients
- Participating on the Steering Committee and all active subcommittees

Network Coordinator
In collaboration with the Program Scientist, the Network Coordinator participates in the development and overall program management of the Network. The Network Coordinator serves as the liaison between Network collaborators, facilitating collaboration between NICHD Program Officials, Clinical Centers, the Data Coordinating Center, and Grants Management.

The NICHD Network Coordinator has primary responsibility for coordination of NRN activities, including:

- Facilitating communication among PIs, coordinators, the data coordinating center, and NICHD
- Working with the Grants Management Specialist, Program Scientist, and data coordinating center to prepare budgets and projections, as needed
- Assist in developing budgets for Network protocols, as needed
- Assisting the DCC with coordinating the Steering Committee meeting agenda, subcommittee meetings, protocol training, and other meetings, as needed
- Assisting in preparing and maintaining all official study documentation, including the NRN Policy and Procedures Manual, communications with the FDA, and related study documentation
- Tracking Network publications, in conjunction with the Publications Subcommittee chair, including monitoring required submission of NRN publications to PubMed Central and providing data for updates to the Steering Committee and/or NICHD
- Tracking proposed concepts and protocols in the NRN protocol development process, including providing data for updates to the Steering Committee and/or NICHD
- Facilitating center compliance with Federal regulations
- Maintaining the NICHD files for the Network

NICHD Grants Management Officer and Grants Management Specialist
The Grants Management Specialist (GMS), under the supervision of the Grants Management Officer, and is responsible for the day-to-day business management and other non-programmatic aspects of

the NRN. The GMS advises the Program Officer on the development and review of Network policies and procedures. In addition, he/she provides advice on the development and enforcement of new and existing policies and collaborates closely with the Network Coordinator to develop annual awards, capitation budget, and periodic adjustments to awards. The GMS ensures that award recipients comply with all legal, regulatory, and policy requirements, reviews and ensures that Letters of Agreement and other contractual agreements are sound, reviews grant applications, analyzes budgets and funding proposals, negotiates funding levels and terms of awards with grantees, and issues finalized grant awards.

Chapter

3

Organizational Structure

This section details the roles and responsibilities of the NRN Steering Committee, DSMC, and Advisory Board, as well as subcommittees established by the Steering Committee.

Overall responsibility for program management, review, and oversight of the NRN cooperative agreements resides with NICHD. Additional Network governing bodies have been established to provide in-depth scientific evaluation and support:

- NRN Steering Committee
- Data and Safety Monitoring Committee (DSMC)
- Advisory Board

In addition, the Steering Committee has established several standing subcommittees, protocol subcommittees, and working groups as detailed in this Chapter.

3.1 NRN Steering Committee

Purpose

The purpose of the Steering Committee is to fulfill the objective of the Neonatal Research Network to "facilitate the advancement of neonatal care by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, can study the required numbers of patients and can provide answers more rapidly that individual centers acting alone." The Steering Committee assures compliance with Network policies and procedures; selects topics for investigation; designs study protocols; implements studies; participates in the analysis and interpretation of data; and reports results in presentations and publications.

The NRN Steering Committee retains "custody and [has] primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies."

Membership

Steering Committee consists of:

- Principal investigator from each Clinical Center (voting members)
- Principal investigator from the Data Coordinating Center (voting member)

- NICHD Program Scientist (voting member)
- Steering Committee chairperson, appointed by the Director of NICHD (tie-breaking vote only)

The chairperson is appointed by the Director of the NICHD. In cases of a tie vote, the chairperson casts the tie-breaking vote.

Responsibilities

The NRN Steering Committee has primary responsibility for the development and implementation of protocols and the preparation of publications. As such, it selects topics for Network research (within the constraints of the budget), and oversees the development, implementation, monitoring, and publications of NRN studies and trials.

The Steering Committee is generally not allowed to release study data until two years after publication of the primary paper from ongoing clinical trials. In certain instances, even extending beyond the 2-year guideline, data may not be released secondary to programmatic decisions.

Meetings and Attendance

The Steering Committee is convened face-to-face 3-4 times per year and has regularly scheduled teleconferences monthly. Dates for the two- or three-day meetings are scheduled 6-12 months in advance. Attendees include all Steering Committee members, along with the NICHD Network Coordinator, NRN research coordinators, the DCC Coordinator, and other DCC staff members.

Attendance at Steering Committee meetings, for the entire 2-3 day meeting, is mandatory for all voting committee members – the input of each principal investigator is fundamental to the operation and advancement of the Network. Should a PI not be able to attend a Steering Committee meeting, he/she is required to notify the Program Scientist of the expected absence, and ensure the attendance of the alternate PI or his/her designee. The research coordinators of each center are required to attend at least two Steering Committee meeting per year.

Follow-up PIs are expected to meet semi-annually – usually during the October Steering Committee meeting and during the Pediatric Academic Society annual meeting to discuss issues and concerns and attend necessary training and certification sessions.

Center principal investigators are permitted to invite their Alternate PIs, Follow-up PIs, and/or other clinical center professionals with special interest and expertise relevant to the meetings, pending approval from the Program Scientist. Investigators leading ongoing NRN studies should regularly attend Steering Committee meetings to update the committee on study issues. Special consultants and guests may be invited to attend Steering Committee meetings at the invitation and approval of the NICHD Program Scientist.

In addition, the NICHD Program Officer, Grants Management Officer, Grants Management Specialist, Director of the Center for Developmental Biology & Perinatal Medicine, and the staff of the Pregnancy and Perinatology Branch may also be invited to attend the Steering Committee meetings as non-voting participants.

Agenda

Before the meeting the DCC will distribute an agenda to the Steering Committee.

The first day's agenda typically includes subcommittee meetings and concept and proposal presentations for new protocols. The second day's agenda typically includes short presentations to the full Steering Committee from the chairs of each protocol subcommittee, plus the standing subcommittees, followed by an update on the overall Network from the DCC. Meetings may also include training sessions for upcoming protocols. One meeting per year, normally in the Fall, includes a third day for discussion and presentation of Follow-up Study issues and re-certification training. As needed, the Program Scientist may ask expert consultants or guests to make special presentations.

The Steering Committee meeting agenda is usually very full. Each meeting has a limited number of timeslots open for presentations of concepts and proposals. Slots are assigned on a first-come, first-serve basis. See Chapter 5, Protocol Review, for details.

Presenters must email any handouts for distribution at the meeting to the Program Scientist and DCC Coordinator *at least one week prior to the meeting* to ensure adequate time to make the necessary photocopies. Concept and proposal materials must be submitted at least six weeks prior to the meeting to allow Steering Committee members adequate time to read and critique the proposals – delays in distributing the materials may lead to delays in Steering Committee votes on the proposals. See Chapter 5, Protocol Review, for concept and protocol deadlines.

3.2 Data Safety Monitoring Committee

Purpose

The Data Safety Monitoring Committee (DSMC) is "responsible for safeguarding the interests of study participants and assessing safety...to protect the study participant from unacceptable risk." The DSMC advises NICHD on research design and data quality and analysis issues pertaining to interim monitoring for safety and efficacy, and ethical and human subject aspects of studies. See the DSMC Charter in Appendix B for details.

Membership

The Director of NICHD appoints members, including a committee chair and vice chair, in accordance with established NIH policies. Members of the Data Safety and Monitoring Committee include experts in neonatology, maternal-fetal medicine, ethics, clinical trial design, biostatistics, and basic science, along with a standing NICHD representative. A NICHD representative, who is not part of the Network, participates in the deliberations, but does not vote. He or she is present to represent NICHD's points of view and to report the DSMC's deliberations to the NICHD Director. Additional ad hoc members may be appointed to supplement the expertise of the DSMC for specific protocols at the discretion of NICHD. Ad hoc members only have voting rights for those protocols for which they advise. See Appendix B for a current roster.

Responsibilities

The DSMC meets regularly to review the ongoing and upcoming protocols with respect to ethical and safety standards. It monitors the safety of ongoing clinical trials and advises the NRN on study conduct. The DSMC provides recommendations to the Director of NICHD about starting, continuing, and stopping randomized clinical trials in the Neonatal Research Network. All data distributed to the DSMC and deliberations of the DSMC are strictly confidential. Decisions to alter or halt studies are the responsibility of the Director of NICHD. The DSMC may recommend protocol modifications based on concerns for patient welfare or scientific integrity. The committee is privy to statistical data and adverse events that it may require for its deliberations. It reviews interim reports of patient accrual and outcome measures provided by the Data Coordinating Center.

Meetings and Attendance

The DSMC meets in person at least once every year. Additional meetings, usually via teleconference, are scheduled based on protocol needs and adverse events.

Agenda

Face-to-face meetings generally include an open session and a closed session. During the open session, the NICHD Program Scientist updates the DSMC on the status of ongoing trial(s) and any upcoming clinical trials. Open sessions may include a review of new research protocols.

Following meetings, the Data Coordinating Center drafts the meeting minutes and sends them to the DSMC Chairman for his approval. The minutes are then forwarded to the NICHD Program Scientist for distribution. This report summarizes important findings of the studies undertaken by the Network and may include recommendations for protocol or procedural changes. If needed, the DCC prepares a brief report of each meeting and transmits it to NICHD which provides the information to the Steering Committee to be forward to the chair of the Investigational Review Board(s) (IRBs) at each site.

3.3 Advisory Board

Purpose

The Advisory Board is an external peer review group whose primary purpose is to advise NICHD and the Neonatal Research Network in the identification and prioritization of topics for Network research. The board provides advice to the Steering Committee on the scientific merit and potential impact of proposed studies. A roster of the current Advisory Board members is included in Appendix C.

Membership

The Director of NICHD appoints the members of the Advisory Board. It is composed of individuals with expertise in clinical trials, biostatistics, epidemiology, maternal-fetal medicine, and neonatology. The NRN Steering Committee Chairperson serves as an advisor to the Advisory Board. Consultants with specific expertise participate as necessary.

Members of the Advisory Board are separate and distinct from the DSMC.

Responsibilities
The Advisory Board is responsible for identifying and prioritizing topics for network research. It reviews preliminary protocols for concept clearance and provides formal review and critique of all final protocols prepared by protocol subcommittees, approved by the Steering Committee, and reviewed by external reviewers. Final drafts of Network primary studies are distributed to the Advisory Board for comment before publication submission. The Advisory Board meets with the Steering Committee, as needed, to provide comments directly to the investigators.

Meetings
The Advisory Board reviews protocols as needed.

3.4 NRN Subcommittees

The Steering Committee has established several standing subcommittees, protocol subcommittees, and working groups.

Membership
Subcommittees are composed of approximately six members each, in addition to the NICHD Program Scientist and the DCC PI (or his/her designee). Principal Investigators, as well as other study investigators, from the clinical centers generally comprise the remaining members of the standing subcommittees. Every protocol subcommittee includes 1-2 coordinators. Members of the subcommittees elect a subcommittee chairperson and a vice chairperson, preferably at least one of which is a voting member of the Steering Committee. The vice chair provides continuity in the absence of the chairperson.

Member preference is used as the basis for subcommittee selection; however, because of the cooperative nature of the NICHD Neonatal Research Network and the demands of the protocol subcommittees, members are ordinarily restricted, based on the total number of PIs and subcommittees, to service on two standing subcommittees. The Steering Committee Chairperson and NICHD Program Scientist periodically evaluate the composition of subcommittees and use that information as a selection criterion when establishing membership of new subcommittees and when filling vacancies.

In addition to NRN participants, members of the subcommittee or Steering Committee may nominate non-Network individuals with special expertise to participate on a subcommittee as a consultant. Consultants must be approved by the subcommittee chairperson, the NICHD Program Scientist, and the Steering Committee. In addition, Program Officials with relevant expertise from other NIH institutes and/or government agencies (e.g., CDC) may be enlisted to serve on a subcommittee with the approval of the subcommittee chairperson and the NICHD Program Scientist.

Vacancies on subcommittees are filled at the discretion of the NICHD Program Scientist, based on recommendations from the Protocol Subcommittee Chairperson.

If a protocol subcommittee member is no longer affiliated with a Network center – either because he/she has left the Network center or the center does not successfully re-compete – and he/she was active in the development and implementation of the protocol, he or she may remain a member of the subcommittee at the discretion of the subcommittee and NICHD Program Scientist. Non-affiliated investigators cannot be members of a standing subcommittee.

In the event that a Protocol Subcommittee Chairperson is no longer affiliated with a current Network center, yet wants to continue in this position and is an active participant (as determined by the NICHD Program Scientist), the Subcommittee Chairperson may be approved to continue as the subcommittee's chairperson. In this case, one of the remaining Center PIs may be voted as vice chair for the duration of the subcommittee.

A roster of the current subcommittee membership is available on the NRN intranet website.

3.5 Standing Subcommittees

Standing subcommittees provide leadership for the ongoing scientific efforts of the Network. The standing subcommittees are listed below and described in detail in the following sections.

Administrative standing subcommittees include:

- Protocol Review Subcommittee
- Publications Subcommittee
- Abstract Review Subcommittee
- Coordinator Liaison Subcommittee
- Concurrent Research Subcommittee
- Data Access Subcommittee
- MFMU Liaison Subcommittee
- Subcommittee on Subcommittees

Study-related standing subcommittees include:

- Generic Database (GDB) Subcommittee
- Follow-up Protocol (FU) Subcommittee
- Genomics Subcommittee

For all subcommittees, the Subcommittee Chairperson assumes leadership responsibility for his/her subcommittee, but must work collaboratively with the other members of the subcommittee. He or she is responsible for:

- Monitoring overall progress of the subcommittee to meeting its responsibilities
- Ensuring an equitable division of labor in duties among the subcommittee members

- Convening meetings and conference calls, as needed, and developing and distributing agendas for the same (with assistance from the DCC, as needed)
- Updating the Steering Committee on subcommittee and/or study activities, including making presentations at all Steering Committee meetings

The NICHD Program Scientist maintains the authority to convene a subcommittee, and will notify the subcommittee chairperson of this, as needed.

Should differing opinions arise, following discussions, subcommittee members must vote on the issue, with the majority vote ruling.

Meetings and Attendance
The major standing subcommittees – Protocol Review, Publications, Coordinator Liaison, GDB, FU, and Genomics – meet either face-to-face or via teleconference at least once per quarter, with additional meetings scheduled as needed. The Concurrent Research, Data Access, and Subcommittee on Subcommittees convene as relevant issues arise. As with the Steering Committee, attendance at subcommittee meetings must be given the highest priority by its members – the input of each member is fundamental to the efficient operation of the overall subcommittee.

3.5.1 Protocol Review Subcommittee

Purpose
The purpose of the Protocol Review Subcommittee is to review and refine protocols for Steering Committee approval.

Membership
Because of the demanding nature of this subcommittee and the need to allow fair and equal representation of all centers, the membership of this subcommittee rotates periodically. It includes approximately six center PIs, the DCC PI, and the NICHD Program Scientist.

Responsibilities
Upon receipt of a draft protocol, the Protocol Review Subcommittee chair and the NICHD Program Scientists review the protocol for all required elements. If the protocol has all the required elements, it is forwarded to the Protocol Review Subcommittee for review. Approximately three members are assigned to prepare formal written reviews of the design and feasibility (similar to the NIH review process). The reviewers present their reviews on a Protocol Review Subcommittee conference call; all members discuss the protocol and come up with recommendations. See Chapter 5 for details on the protocol review process.

Meetings and Attendance
The Protocol Review Subcommittee meets generally 6-12 times per year, usually via teleconference, to review draft protocols that are in process. Additional teleconferences are scheduled as needed to review specific draft protocols.

3.5.2 Publications Subcommittee

Purpose
The purpose of the Publications Subcommittee is to ensure the timely preparation of high-quality presentations and publications from the Network.

Membership
Members of this committee include approximately four Center PIs, the DCC PI, the NICHD Program Scientist, and the NICHD Network Coordinator.

Responsibilities
The Publications Subcommittee is responsible for:

- Developing and implementing the NRN's publication policy
- Conducting internal peer reviews of all NRN manuscripts prior to submission for publication

For details on the NRN Publication Policy and process, see Chapter 6.

Meetings and Attendance
The Publications Subcommittee meets quarterly, usually via teleconference just prior to the Steering Committee meetings, to review the status of manuscripts that are in process. Additional teleconferences are scheduled as needed.

3.5.3 Abstract Review Subcommittee

Purpose
Similar to the Publications Subcommittee, the purpose of the Abstract Review Subcommittee is to ensure the preparation of high-quality presentations from the Network at the PAS annual meeting. Abstracts for other meetings usually go to the Steering Committee for review and approval.

Membership
The members of the Abstract Subcommittee include: the chairs of the Steering Committee, Protocol Review, Publications, GDB, and Follow-up Study Subcommittees, the DCC PI, and the NICHD Program Scientist.

Responsibilities
The Abstract Subcommittee is responsible for reviewing and approving proposals for data analyses for submission to the PAS annual meeting, ensuring that they are unique, well-designed, and potentially worthy of publication in a peer-reviewed journal prior to submitting the requests to the DCC. This review occurs after the relevant protocol subcommittee(s) have reviewed and approved the proposals.

Meetings and Attendance
The Abstract Subcommittee meets as needed to review abstract proposals. Proposals are normally due in July of each year, with final approval decisions made by late Summer to give the DCC sufficient time to process analysis requests before the PAS submission deadline in late Fall.

3.5.4 Coordinator Liaison Subcommittee

Purpose
The purpose of the Coordinator Liaison Subcommittees is to discuss the concerns of the NRN research coordinators and communicate them, along with recommendations for action, to the Steering Committee.

Membership
Members of this subcommittee include approximately four site coordinators, the DCC Coordinator(s), and the NICHD Network Coordinator.

Responsibilities
The Coordinator Liaison subcommittee is responsible for communicating issues between the NRN coordinators and the Steering Committee. It:

- Discusses issues regarding ongoing trials and the implications of upcoming studies from the coordinator's perspective, raising issues or concerns particularly related to protocol implementation and IRB approval
- Communicates any concerns and makes recommendations to the Steering Committee and/or Study PI
- Organizes a monthly teleconference with the NRN coordinators to discuss their concerns
- Conducts the Coordinators meeting at the Steering Committee meetings
- Mentors new site coordinators, as needed, regarding ongoing NRN protocols, policies, and processes

In addition, the Coordinator Liaison subcommittee may propose topics for research (e.g., Antenatal Consent) or for analysis of existing study data.

Meetings and Attendance
The Coordinators Subcommittee meets as a subcommittee as needed. It holds monthly teleconferences with all NRN Coordinators to discuss concerns as they arise. These calls generally include the study PIs of ongoing or soon-to-be initiated studies and trials. The subcommittee also conducts a meeting of NRN Coordinators at each Steering Committee meeting to discuss issues and concerns. The chair reports the issues raised to the Steering Committee.

3.5.5 Concurrent Research Subcommittee

Purpose
The purpose of the Concurrent Research Subcommittee is to review non-NRN protocols and make recommendations regarding potential conflicts or compatibility with Network protocols.

Membership
Members of this subcommittee include approximately four Center PIs, the DCC PI, and the NICHD Program Scientist.

Responsibilities
The Concurrent Research Subcommittee is responsible for:

- Surveying each center annually for ongoing or planned non-Network clinical research (to be submitted on an Additional Site Studies Questionnaire)
- Evaluating whether ongoing or planned non-Network research at participating NRN centers is likely to affect recruitment, introduce confounders into the results, or otherwise impede the implementation or analysis of ongoing or planned NRN research
- Making recommendations to the Steering Committee based on the evaluation

Meetings and Attendance
The Concurrent Research Subcommittee meets as needed.

3.5.6 Data Access Subcommittee

Purpose
The Data Access Subcommittee oversees the NRN's policy on data requests and reviews requests for data access from Network and non-network investigators as needed.

Membership
Membership of the Data Access subcommittee consists of approximately five Center PIs, the DCC PI, and the NICHD Program Scientist.

Responsibilities
The Data Access subcommittee reviews and responds to requests for data from external parties, following guidelines approved by the Steering Committee and NICHD. Requests are generally handled via email.

Meetings and Attendance
The Data Access Subcommittee meets as needed.

3.5.7 MFMU Liaison Subcommittee

Purpose
The MFMU Liaison Subcommittee is part of a joint Liaison Committee of the Maternal-Fetal Medicine Units (MFMU) Network and the Neonatal Research Network. The joint committee's purpose is to improve collaboration and facilitate communication between the two groups.

Membership
NRN members of this committee include: four NRN Site PIs, the NRN DCC PI, and the NICHD NRN Program Scientist.

Responsibilities
The Liaison Committee is responsible for:

- Communicating ongoing and planned research and research results of the two Networks at each other's Steering Committee meetings
- Notifying the MFMU and NRN Program Scientists immediately if a potential conflict is discovered.

Meetings and Attendance
The MFMU Liaison Subcommittee meets as needed. A representative from the subcommittee is assigned to attend each MFMU Steering Committee meeting. At that meeting, he or she presents ongoing and planned NRN research that may be of interest to the MFMU.

3.5.8 Subcommittee on Subcommittees

Purpose
The purpose of the Subcommittee on Subcommittees is to evaluate and recommend policies governing both the standing and protocol subcommittees.

Membership
Members of this subcommittee include approximately five Center PIs, the DCC PI, and the NICHD Program Scientist.

Responsibilities
The Subcommittee on Subcommittees is responsible for:

- Reviewing subcommittee function to ensure that they operate effectively
- Presenting specific and/or unique issues to the Steering Committee for guidance and approval

Meetings and Attendance
The Subcommittee on Subcommittees meets as needed.

3.5.9 Generic Database Subcommittee

Purpose
The purpose of the GDB Subcommittee is to create and maintain a uniform Generic Database, which: provides data to characterize the infants admitted to the clinical centers; examines the relationships between defined entry characteristics and outcome; measures trends in the incidence of various disease entities; and provides data for hypothesis generation and trial design for future Network studies.

The Generic Database is a registry of very low birth weight infants born alive in NRN centers. The GDB collects observational baseline data on both mothers and infants, the therapies used and the outcomes of the infants. Data are analyzed to find associations and trends between baseline information, treatments, and infant outcome, and to develop future NRN trials.

Membership
Membership of the GDB Subcommittee consists of approximately four Center PIs, two coordinators, the DCC PI, and the NICHD Program Scientist.

Responsibilities
The GDB Subcommittee is responsible for:

- Managing the content of the GDB
- Designing the GDB data forms and manual to ensure that data are collected in a uniform manner
- Reviewing and approving requests for data or data analyses using the Generic Database, ensuring that proposals for analyzing GDB data (e.g., for abstracts or manuscripts) are unique and well-designed prior to submitting them to the DCC.
- Reviewing requests to revise or change GDB data collection, in conjunction with the Protocol Review Subcommittee, and making recommendations to the Steering Committee regarding proposed changes

See Chapter 5 for details on the process for making revisions and additions to the GDB.

Meetings and Attendance
The GDB Subcommittee meets quarterly, usually prior to Steering Committee meetings, to discuss issues and concerns. Additional teleconferences are scheduled as needed.

3.5.10 Follow-Up Protocol Subcommittee

Purpose
The purpose of the Follow-Up Protocol Subcommittee is to review proposed FU secondary protocols and proposed changes to the FU Study protocol, manual, and forms.

Membership
Members of the FU subcommittee include Follow-Up PIs, the DCC PI, and the Program Scientist.

Responsibilities
The Follow-Up Protocol Subcommittee is responsible for:

- Designing the FU data forms and manual to ensure that data is collected in a uniform manner
- Reviewing and approving proposals for analyzing the data (e.g., for abstracts or manuscripts).

- Reviewing requests to revise or change FU data collection, in conjunction with the Protocol Review Subcommittee, and making recommendations to the Steering Committee regarding proposed changes (see Chapter 5 for details)
- Proposing topics for research requiring FU or for analysis of existing study data.

Meetings and Attendance
The FU Study Subcommittee meets as needed to discuss issues and concerns. Additional teleconferences are scheduled as needed.

3.5.11 Genomics Subcommittee

Purpose
The purpose of the Genomic Subcommittee is to advise the Steering Committee in areas pertaining to genetic research in the Network.

Membership
Membership of the Genomics subcommittee consists of: approximately five Center PIs, the DCC PI, and the NICHD Program Scientist. Ad hoc members may be invited to join at the discretion of the Program Scientist and Subcommittee Chair, subject to Steering Committee approval.

Responsibilities
The Genomics Subcommittee is responsible for:

- Evaluating protocols involving genomics for both merit and feasibility
- Developing potential genomics tissue repositories of existing NRN samples and data, and developing guidelines for their use
- Monitoring and guiding the ethical standards of genomics research in the NRN
- Developing panels of ad hoc advisors for scientific and ethical issues implicit with genomics research in the neonate, as needed

Meetings and Attendance
The Genomics Subcommittee meets quarterly and as needed.

3.6 Protocol Subcommittees

Purpose
Once the Steering Committee approves a protocol, it appoints a protocol subcommittee, whose purpose is to manage the implementation of the protocol and any approved secondary protocols, and publish the results.

For secondary studies, unless special expertise is required, the original protocol subcommittee serves as the secondary protocol subcommittee. If a secondary protocol requires specific expertise, the Protocol Subcommittee and the Steering Committee may approve the formation of a special subcommittee that will collaborate with the original protocol subcommittee for this purpose.

Membership

Protocol subcommittees consist of approximately four Center PIs or their designees, 2 center research coordinators, the DCC PI or his/her designee, and the NICHD Program Scientist – 50 percent of the membership must be Steering Committee members, including the NICHD Program Scientist and DCC PI. At least one research coordinators must serve on each trial subcommittee. If the protocol includes Follow-up as a primary outcome, then a FU PI is included on the subcommittee. The author of the original concept – the Study PI – usually becomes the protocol subcommittee chairperson and lead author of any resulting primary study publication(s). The Protocol Subcommittee must elect a subcommittee vice chair.

In general, subcommittee membership is based on PI interest; however, Center PIs are generally restricted to serve on no more than two active protocol subcommittees at any one time. After receiving input from Steering Committee members, the NICHD Program Scientist, in consultation with the Study PI, is charged with making final determination of subcommittee assignments.

Active subcommittee membership defines primary authorship of any resulting publications, as described in Chapter 6, Publications.

Responsibilities

As delegated by the Steering Committee, protocol subcommittees are responsible for:

- Developing the final protocol, manual, and data forms for the main study and any pilot or secondary studies
- Modifying the protocol to meet the recommendations of the Steering Committee, Advisory Board, external reviewers, and Data and Safety Monitoring Committee
- Working with the DCC to finalize and program data forms, order any necessary equipment and supplies, and set up other logistical procedures (i.e., randomization procedures) necessary for study implementation
- Monitoring clinical performance (recruitment, protocol adherence, randomization, delays in completing data forms, data quality, responsiveness to edits and audits, etc.), including working one-on-one with individual sites to improve performance as needed
- Advise the Steering Committee of issues that arise during study implementation
- Recommending procedural changes to the Steering Committee to improve clinical performance
- Reviewing and making recommendations to the Steering Committee regarding all secondary or ancillary proposals to the main protocol
- Working with the DCC to analyze results for the pilot, main, and any secondary studies
- Publishing study results for the main study and any secondary studies, as well as any appropriate pilot studies
- Reviewing and making approval recommendations regarding proposals to analyze or use study data for abstracts, presentations, and manuscripts, including proposals made by non-subcommittee members.

Meetings and Attendance
Protocol subcommittees and working groups meet as needed. In general, during the design and initial implementation phases, a subcommittee holds regular teleconferences to discuss revisions of the protocol, manual, and forms. During implementation, the subcommittee meets face-to-face in conjunction with the Steering Committee meetings. During the analysis and manuscript drafting phases, the subcommittee holds teleconferences as needed to discuss the results and review drafts of proposed abstract(s), presentation(s), and/or manuscript(s). The DCC will distribute any requested recruitment or analysis reports to the subcommittee chair before meetings or calls.

As with the Steering Committee, attendance at subcommittee meetings must be given the highest priority by its members – the input of each member is fundamental to the development and implementation of the study. Coauthors on the publication are expected to participate fully in subcommittee discussions, as per the Publication Policy (see Chapter 6 for details).

3.7 Working Groups

Purpose
Prior to approval of a full protocol, the Steering Committee can establish a working group, whose purpose is to develop a specific proposal from an approved concept to a full protocol.

Membership
Membership of a working group varies depending on the nature of the study.

Responsibilities
Working groups are responsible for:

- Developing a draft protocol and submitting it to the Protocol Review Subcommittee
- Presenting the protocol to the Steering Committee for its approval

Meetings and Attendance
Working groups hold regular teleconferences to discuss protocol development.

Chapter

4

Standard Operating Procedures

4.1 Quality Assurance and Control

The NRN has developed a number of procedures to ensure that Network's studies collect data of the highest quality possible. Procedures range from weekly editing of the data by the DCC to site visits to review and evaluate research procedures and organization. Edits display missing or incongruent information on a particular participant's data form (intraform check). Audits check for accuracy and congruency of information across all data forms for an individual participant (interform check). Clinical centers are routinely notified and requested to review data, as needed.

4.1.1 Monthly Reports

The DCC generates and distributes a monthly report of ongoing Network studies and trials to the Steering Committee. This report details, as relevant, the number of subjects eligible, recruited, randomized, withdrawn, and seen in follow-up for each ongoing study by Network center. The report also details outstanding edits needed from each center by study. Report numbers are based on study data successfully transmitted to the DCC by the last day of the previous month.

4.1.2 Site Visits

Site visits are performed as needed by the Data Coordinating Center, NICHD Program Scientist, and a research coordinator to ensure data quality and regulatory compliance, and to evaluate the performance of center investigators and staff. NICHD and the DCC develop the agenda, with input from the Clinical Site, to include: a standardized chart review; inspection of facilities, personnel, and records; pharmacy review; and organizational review. NICHD distributes the results, with suggestions for potential opportunities for improvement, to the Clinical Center. See Appendix D for a sample site visit agenda.

The purpose of a site visit is to:

- Review Network procedures with the clinical center's Principal Investigator and relevant staff
- Assess the center's proficiency in executing Network protocols, including study recruitment and follow-up
- Assess the center's data quality

In addition, the site visit team can use the on-site meeting to identify and solve problems emerging from such assessments and/or transfer effective practices from other clinical centers.

For the chart review, the DCC will select a set of patient charts to be reviewed and provide a list of these to the clinical center and NICHD Program Scientist. The clinical center can prepare for the audit by ensuring that the original charts are available for the site visit. At the time of the site visit, research staff that completed the original data forms for the selected charts should be available. The Site Visit Team will examine the charts, specifically looking for:

- Data entry accuracy
- A signed copy of the informed consent
- Eligibility criteria
- Lost to follow-up
- Data completion procedures
- Protocol violations
- Any specific protocol requirement, such as documentation of laboratory test results.

Following the site visit, NICHD and the DCC will write a site visit report detailing the team's overall assessment of the clinical center, with specific emphasis on problem areas, looking at::

- Staff and Facilities
- Organizational Procedures
- Protocol Procedures
- Data Quality

If needed, the report will include recommendations and a log of specific data queries emanating from the chart review that must be either corrected or verified as correct. The log must be returned to the DCC with each query answered. The clinical center PI will be asked to respond in writing to the Site Visit Report within a designated timeframe, particularly addressing areas of concern observed by the team and the recommendations.

4.2 Budget and Fiscal Management

Awards for the Clinical Center and the Data Coordinating Center are made using the U10 cooperative agreement mechanism. Awards to the Clinical Centers include a base budget covering salaries and administrative costs. The DCC's award includes both a base budget and a capitation budget covering protocol implementation expenses.

Beginning in April 2010, the Data Coordinating Center is responsible for setting up subcontracts or other agreements with the clinical centers. In accordance with these, the DCC provides reimbursement for capitation-related expenses.

As detailed in Chapter 5, the Steering Committee approves a protocol's budget in a Budget Priority Vote, and each Center thereby agrees to accept the budget, pending availability of NICHD funding.

New Clinical Centers are required to accept protocol budgets for studies already underway in the Network. Clinical site researchers are encouraged to assist in the development of protocol budgets.

Total funding for Clinical Centers depends on the base awards and reimbursements for approved protocol-related expenses from the DCC. The overall provision of money for the NRN Network is subject to availability of NICHD funding.

4.2.1 Base Budget

As outlined in the Clinical Center RFA, NICHD awards a base budget to each clinical center to cover NRN-related research. This includes money for salaries, supplies, other expenses up to the RFA-specified limits plus travel expenses to attend the NRN quarterly meetings. Funding for the applicable Facilities and Administrative (F&A) Costs is also provided. The DCC provides clinical centers with computer hardware and software for Network data entry and transmission.

4.2.2 Capitation Budget

Beginning April 1, 2010, protocol implementation costs are covered under a Capitation Budget awarded to the DCC.

Protocol budgets consist of:

- Specific protocol-related expenses to be funded on a per capita (per subject enrolled or randomized) basis covering such costs as research staff time, drug and other supplies, subject incentives, etc.
- Study expenses such as pharmacy start-up, specimen shipping, training, equipment, etc.
- Estimated indirect rates.

Project year
The grant project period is currently from April 1st to March 31st.

Capitation rates
During protocol development, the study PI, working with the Steering Committee, develops a protocol budget to include recruitment and implementation costs for necessary night, weekend, and holiday coverage, based on the average estimated research coordinator time required to get consent, conduct study activities, and collect data. This could potentially include the cost of study-specific drug administration, sample collection, processing, and testing that is not included in standard patient care. The final capitation rate is agreed to as part of the Steering Committee's Budget Priority vote.

Reimbursement
Based on each center's actual recruitment in a project year, the DCC will issue reimbursements to the Clinical Centers for NRN-approved protocol expenses at the agreed upon rates. Each protocol manual specifies what constitutes "recruitment" or "enrollment" in terms of specific forms completed and successfully transmitted to the DCC within that project year.

Projected Enrollment
For new protocols, targets are established for projected recruitment by estimating the number of patients a center is likely to recruit during the budget period. This estimate may be based on information from the GDB and/or gathered from each center during protocol development.

Budget management
To manage the NRN capitation budget, the DCC may establish a recruitment limit for each Clinical Center for each protocol. If a Clinical Center believes that it will exceed its enrollment target for any particular protocol for that year, when it reaches 80 percent of its projected recruitment, the clinical site PI or his/her designee must notify the DCC in writing for permission to enroll beyond that target. The DCC's permission must be granted before additional reimbursable recruitment over the enrollment target can take place.

The DCC will make sure capitation expenses do not exceed available funding each fiscal year.

4.2.3 Financial Status Reports and Carryover Requests

Financial Status Reports
Grantee institutions are required to submit a Financial Status Report (FSRs) to the NIH. FSRs report expenditures and any unobligated balances remaining in a grant for the budget period. According to NIH procedures Financial Status Reports must be submitted via NIH's eRA Commons website (https://commons.era.nih.gov/commons) within 90 days after the end of the budget period. Timely submission of the FSR is mandatory for continued funding. See the NIH Grants Policy Statement (available at http://grants.nih.gov/grants/policy) for details.

Carryover Requests
An approved carryover gives grantees the expanded authority to use grant funds from one budget period in the next budget period. As per the NIH Grants Policy Statement, cooperative agreement (U) awards are excluded from automatically carrying over unobligated balances. Grantees must specifically request and receive approval to carry over unobligated funds.

A FSR for the given budget period must be completed and accepted by NIH before an institution can submit a carryover request for that budget period.

4.2.4 Monitoring and Evaluation

Continued membership in the Network is dependent upon active and successful participation. NICHD reviews NRN centers annually, based on recruitment reports, site visits, and performance reports. The DCC provides data for these reports from the NRN data management system, including racial and gender breakdown of subjects for NIH population tracking. The evaluation of participation and justification of capitation funds is based on both quantitative elements (successfully enrollment and protocol implementation, successful follow-up) and qualitative elements (timeliness of protocol initiation, quality and timeliness of data entry, etc.).

4.2.5 K Awards and MSCIDAs

K Award Network projects
In an effort to continue to move science forward and provide valuable resources for potential clinician investigators and physician scientist candidates, concurrent Network projects and K awards (Mentored Research Scientist Development Awards) can be considered under specific circumstances:

- A potential K award applicant is identified, usually by the NRN Center PI.
- A plan for career development, mentoring, environment, and institutional commitment are formulated at the site.
- The research plan must undergo the same protocol concept and review process and all proposed NRN studies
- There is no financial overlap between the K award and any Network funds.

Timetables may vary depending on grant submission deadlines, feasibility, revision of the research plan, and the K Award application deadline. The NRN approval of the research plan is separate from the NIH grant application and scientific review procedures. If the research protocol is approved by the NRN Steering Committee, a letter will be provided for inclusion in the K award application.

Mentored Specialized Clinical Investigator Development Awards (MSCIDAs)
Periodically, NICHD issues Letters of Invitation (LOI) soliciting applications for MSCIDAs in the NRN. Center PIs may submit an application on behalf of a suitable candidate.

4.2.6 Application for Outside Funding Utilizing Network Patients

Applications for outside support (i.e., non-NICHD funding) are considered on a case-by-case basis by the NICHD Program Official and NICHD Program Scientist with appropriate input and approval from the NRN Steering Committee.

If approved by the Steering Committee, the NICHD Program Scientist writes a letter of support for inclusion in the grant application. NRN approval for the research plan is separate from the grant application and scientific review procedures.

4.3 Data Access

This section covers the Annual NRN Registry Grantee Agreement, Data Request Form(s), Limited Data Set Agreement, and Data Transfer Agreement.

As per the RFA, "The NRN Steering Committee will retain custody and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies."

4.3.1 Annual NRN Registry Grantee Agreements and Data Request Forms

Sites must complete the Data Coordinating Center's Annual NRN Registry Grantee Agreement and Data Request Form prior to receiving their own site's GDB and FU data. The data sent is cumulative (from 1998 to present). GDB data through 2006, for example, typically includes GDB infants that have their primary status (a NG03 or NG03E form) entered into the system, and Follow-up data includes infants whose follow-up window closed 6 months prior to January 1, 2007. Sites can stipulate what format they would like to receive their data in on the Data Request Form (i.e., SAS, SPSS, ACCESS).

The Annual NRN Registry Grantee Agreement and the Data Request Form, along with instructions and contact information, can be found on the NICHD NRN private website under Administrative\Policies and Procedures. Completed forms must be sent to the Data Coordinating Center. Forms may be faxed, scanned, and sent electronically, or sent via FedEx.

4.3.2 Limited Data Set Agreements (for sites who must comply with HIPAA)

Some sites may request a Limited Data Set Agreement between the DCC and the clinical site, primarily for studies conducted at sites that qualify as covered entities under the Health Insurance Portability and Accountability Act (HIPAA). A Limited Data Set cannot contain any direct identifiers, but may contain dates and limited geographic information. These Agreements will generally include HIPAA language and indemnification clauses.

The Limited Data Set Agreement template, along with instructions and contact information, can be located on the NICHD NRN private website under Administrative\Policies and Procedures. The Agreement must be study-specific with all sections modified accordingly. Some sites may prefer to use their own template for this agreement. In either case, the agreement must be reviewed and approved by the site's appropriate institutional office.

Two copies of the Agreement with original signatures must be sent to the Data Coordinating Center. The DCC will review the agreement; if appropriate, the DCC will sign it, keep one of the originals for its records, and return the other fully executed original to the initiating Center.

4.3.3 Data Transfer Agreements

A Data Transfer Agreement is executed when NRN investigators (i.e., PIs, Co-PIs, or Research Fellows) request Network-wide data from the DCC for specific projects. All requests must be pre-approved by the NRN Data Access Subcommittee and/or the relevant Protocol Subcommittee and the Steering Committee.

Once such a request is approved, the site must complete a Data Transfer Agreement Form to enable the DCC to release the data. These forms, along with instructions and contact information, can be found on the NICHD NRN private website under Administrative\Policies and Procedures. The

Agreement must be reviewed and approved by the appropriate institutional office of the recipient institution.

Two copies of the Data Transfer Agreement with original signatures must be sent to the Data Coordinating Center. The DCC will review the agreement; if appropriate, the DCC will sign it, keep one of the originals for its records, and return the other fully executed original to the recipient institution.

4.3.4 Specimen Transfer Agreements

Some protocols require the collection of specimens (blood, urine, cord blood, etc.) as part of study implementation. Protocols that may have extra samples left over should address where and how the specimens will be stored.

To request samples, a study investigator must submit a complete protocol that includes specific hypotheses to be tested, how the specimens will be analyzed, and a statistical analysis plan. The protocol will be reviewed by the appropriate protocol subcommittee(s). The NRN Steering Committee must approve all requests in advance and in writing before any samples may be transferred to the investigator(s).

A Specimen Transfer Agreement should be signed by the specimen repository principal investigator, his/her institution's business official, and the recipient institution's business official, principal investigator, and (if different from the principal investigator) the protocol study investigator prior to any specimens being transferred or analyzed. See Appendix H for details.

4.3.5 External Requests for Data and Information

From time-to-time, the NRN receives requests from non-Network researchers for protocol documents (protocol, manual, and forms) and study data for pre-specified purposes. All requests should be sent to the NICHD Program Scientist for consideration. Generally, data are not released until two years following publication of a primary study.

Depending on the nature of the request, it may go to the Data Access Subcommittee or directly to the Steering Committee. The Steering Committee votes to approve release of the requested information.

The external requestor is asked to acknowledge the use of the NICHD Neonatal Research Network materials in all relevant applications, presentations, and publications.

4.4 Satellite Sites

NRN Clinical Center cooperative agreements are competitively awarded. NICHD selects clinical centers through the NIH scientific review process, based on criteria detailed in a Request for Application. As part of that process, a center can submit an application that includes additional

sites/hospitals. In these cases, the parent institution is responsible for management oversight and performance of NRN research conducted at its satellite hospitals.

4.4.1 Request to Add a Satellite Site

Clinical Centers may add additional satellite sites to their consortium after the cooperative agreement has been awarded. The request to add additional satellite sites must be reviewed and approved by NICHD.

Before NICHD will consider a request to add an additional satellite site, the Clinical Center must meet or exceed the Eligibility Criteria detailed in the RFA.

Note that NICHD will not provide any additional base award funding for satellite sites. The Clinical Center is responsible for establishing financial reimbursements with its satellite sites.

To add satellite sites, the Clinical Center's Principal Investigator and Institutional Business Official must obtain the approval of NICHD and the DCC PI. The Center must submit the following documents to the NICHD Program Scientist, the NICHD Grants Officer, and the DCC PI:

- Written request for approval to add the hospital(s) and/or institution(s) signed by the Center's PI and Institutional Business Official with the Clinical Center's assurance that all federal requirements will be fulfilled
- Copy of the signed contractual agreement with the proposed satellite site
- Implementation Plan for adding the satellite sites, including information on:
    - Funding arrangements
    - Co-authorship agreements
    - Training plan for protocols
    - Anticipated recruitment with recent information on eligible subjects and adequate follow-up rates
    - Staffing and supervisory plans, including cv's for lead personnel, availability of necessary equipment, pharmaceutical arrangements, and follow-up procedures
    - Data management plans, including data entry, handling of data queries and quality assurance
- Federal Wide Assurance (FWA) for the proposed satellite site
- IRB approval and consent forms from the proposed site for each protocol to be conducted at the site, if available

See Appendix E for a sample checklist with further details on the required documentation. Additional documentation or clarification may be requested by the NICHD Program Scientist, NICHD Grants Officer, and/or the DCC Principal Investigator, as needed.

4.4.2 Satellite site approval process

Site Visit

Once the documentation detailed in Section 4.5.1 has been received, the NICHD Program Scientist and the DCC PI and/or his/her representative may conduct a site visit of the proposed facility. At that time, the NICHD Program Scientist or his/her designee will send the Clinical Center an agenda for the planned visit listing the key participants that should attend and remaining issues to discuss. The NICHD Program Scientist will forward a copy of the site report to the Clinical Center PI following the visit.

Approvals

Once all requested documentation and clarifications have been received and a site visit has been conducted, the NICHD Program Scientist and Grants Officer, in consultation with the DCC PI, will determine whether the Clinical Center can proceed with adding the satellite site.

Once an approved site has received its IRB approval(s) and met all of the relevant protocols' certification and training requirements, the Clinical Center will be notified that the site may begin recruiting.

Chapter

5

Protocol Review, Development, and Implementation

In July 2007, the NRN Steering Committee voted to modify the Protocol Review process, adding a Concept proposal stage to encourage and foster the development of new research ideas. The purpose of the revision is for study investigators to get an initial vote of interest from the Steering Committee before they invest the time to develop their research concept into a full protocol.

As detailed in Figure 1 on the next page, the revised Protocol Review Process includes three stages:

1. Concepts
2. Protocol Development Stage
3. Protocol Review and Approval

Progression from one stage to the next is dependent upon Steering Committee approval. Any major changes made to the protocol design at any stage in this process may require it to move back into a prior stage of development and/or go through some or all of the Approval process again. Major changes may include, but are not limited to, changes affecting the study hypothesis, primary outcome, patient population, patient safety, study feasibility, and/or significant increases in the budget.

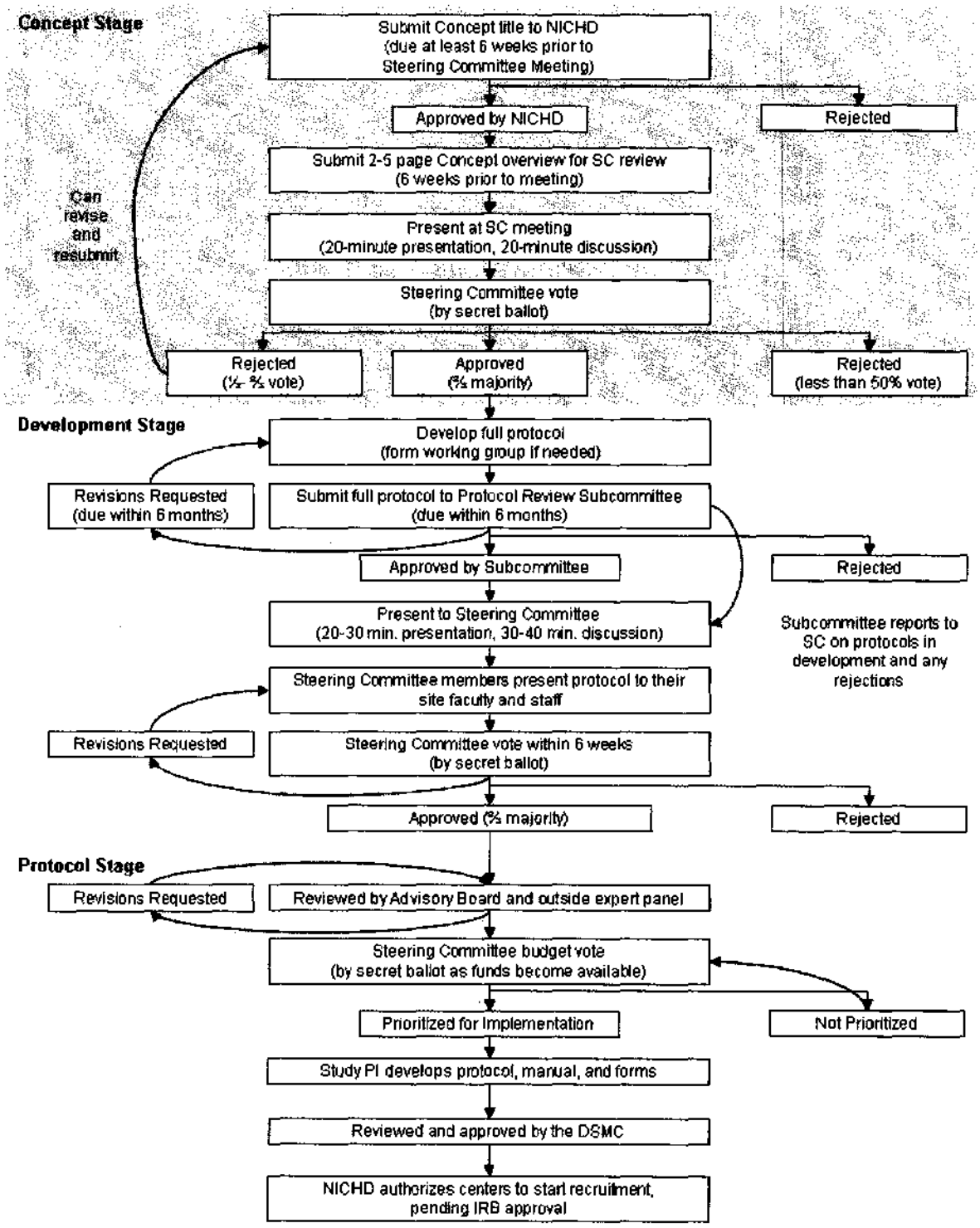
See the Protocol Review flowchart on the next page for an overview.

Secondary protocols and ancillary protocols follow similar processes, as detailed in Section 5.7 and 5.8, respectively.

5.1 Definitions

Primary protocol – Standalone interventional trials or observational studies that are usually prospective in nature. NRN primary protocols may be designed by a member of the Steering Committee or other participants at NRN sites; non-Network PIs must partner with an active NRN site to bring in a concept or protocol for consideration. The protocol author usually becomes the study principal investigator and the chairperson of the study subcommittee.

Figure 1. Neonatal Research Network
Protocol Development Process



Secondary protocol – A study or trial conducted in conjunction with a primary protocol to test a specified hypothesis. Secondary protocols usually involve additional interventions, testing, and/or data collection of the subjects enrolled in the primary protocol. The study population must be either identical to, or a subset of, the subjects in the existing NRN protocol – i.e., no additional subjects are recruited that are not already in the main study. As with primary protocols, secondary protocols may be proposed by a member of the Steering Committee or other participants at NRN sites. The protocol author usually becomes the study PI for the secondary protocol.

Pilot protocol – A study or trial that gathers preliminary data needed for the design of a primary protocol, looking at such issues as feasibility, safety and/or pharmacokinetics. Pilot protocols may be interventional or observational in nature. Pilot protocols are generally proposed as part of a primary protocol.

Ancillary studies – Studies or analyses of subjects enrolled in an existing NRN protocol at a subset of NRN Centers – most often a single-site study. The study population may be identical to, or a subset of, the subjects in the existing NRN protocol. Ancillary protocols are usually designed by a Center PI, his/her alternate PI, or another faculty member at the Center. Ancillary protocols must not interfere with the hypotheses or progress of the primary or approved secondary protocols. NICHD does not generally fund ancillary studies through the NRN.

Secondary analysis – Analysis designed to test a specific hypothesis using data derived from the Generic Database, Follow-Up Study, or other NRN primary or secondary protocols

5.2 Concept

Presentations of research concepts to the NRN introduce innovative topics for collaborative research and stimulate intellectual discussions about the direction and scope of neonatal and follow-up care. Principal and affiliated investigators (alternate PIs, site investigators, or external individuals working with a center PI) can propose new NRN research studies to the Steering Committee. Concept authors should review previous protocols presented to and conducted by the NRN to ensure that new concept proposals are novel and/or address any deficiencies noted in previously proposed/addressed topics. All protocols must be approved by the concerned center PI prior to submission to the NRN for review.

Proposals for secondary protocols to NRN primary studies follow a slightly different procedure. See Section 5.7 for details.

5.2.1 Concept Proposal

The study PI must submit a concept proposal – a 2-5 page overview of the proposed research topic -- to the NICHD Program Scientist *at least 6 weeks prior to the meeting*.

The written concept proposal should be *no more than 5 pages long* and include:

- Section 1: Synopsis. A one-paragraph summary of the proposed research
- Section 2: Hypothesis. The primary hypothesis and research question to be investigated
- Section 3: Background and Significance. A brief summary of supporting research and preliminary studies
- Section 4: Study design. A brief description of how the study would executed including:
    - Study population
    - Inclusion and exclusion criteria
    - Randomized groups (if applicable)
    - Methods
    - Rough estimate of available and required sample size
- Section 5: Budget. An estimate of the direct and indirect costs to the NRN
- Section 6: References

5.2.2 Concept Presentation to the Steering Committee

The Steering Committee meeting has a limited number of timeslots for presentations of new concepts and protocols approved by the Protocol Review Subcommittee. Timeslots are allocated on a first-come, first-serve basis. To reserve a timeslot, the study PI should submit the concept title and/or a brief description in writing to the NICHD Program Scientist for approval at least 6 weeks prior to a Steering Committee meeting. Note: timeslots fill up quickly, so investigators should send the NICHD Program Scientist as much advance notice as possible.

All concept proposals will be posted on the NRN website for Steering Committee members to review prior to the meeting. Presentations to the Steering Committee should be no more than 15-20 minutes long and will be followed by a 20-minute discussion period.

5.2.3 Concept Approval

Following the discussion, the Steering Committee members will vote via secret ballot, considering a broad range of issues, including: study feasibility, ethical considerations, and the importance, novelty, and relevance of the research topic. If ⅔^{rds} of the Steering Committee votes to approve the concept, it can advance to the Protocol Development Stage. If ½ to ⅔^{rds} of the Steering Committee votes to approve it, the concept can be revised and resubmitted. If less than ½ of the Steering Committee approves it, the concept is rejected. The DCC Coordinator will tally the votes for the Steering Committee chairperson and compile any written comments and give them to the study PI.

5.2.4 Research Proposals from Outside the Network

Investigators from non-Network centers and other Institutes of the National Institutes of Health may approach the NICHD Program Scientist with a research proposal for consideration by the Network. The NICHD Program Scientist will discuss the proposal with the Steering Committee to determine if the committee is interested in it and/or if the group would like to see a presentation by the outside investigator. Given the elaborate process to bring a proposal successfully through the Network

process and to implement it, all external proposals require PI sponsorship and must be discussed with the NICHD Program Scientist. If a PI is interested he/she will pursue the research topic with the outside investigator to further evaluate whether he/she wants to sponsor the protocol and to bring it to the Steering Committee. An outside proposing investigator may be appointed as a consultant to the protocol subcommittee if he/she provides a specific expertise requested by the Steering Committee.

5.3 Protocol Development

The concept proposal author usually becomes the study's PI, the person with primary responsibility for protocol development. The study PI develops the initial protocol and submits it to the Protocol Review Subcommittee, which is responsible for the review and refinement of protocols.

If needed, the Steering Committee can establish a working group to assist the Study PI in developing the full protocol. See Section 3.6 for details.

If a pilot study is required (by the Steering Committee, FDA, etc.), the pilot study needs to have its own separate protocol, manual, and forms developed for IRB and other approvals. The pilot study protocol can include information on the broader main study.

5.3.1 Protocol Submission Deadline

Once approved, the concept proposal study PI is responsible for expanding the concept into a full draft protocol and submitting it to the Protocol Review Subcommittee *within 6 months* of the Steering Committee approval vote (unless an extension is authorized by the NICHD Program Scientist).

If a draft protocol is not received within 6 months (and no extension has been granted), the concept will be withdrawn from consideration.

5.3.2 Protocol Working Group

As per Section 3.5, the study PI can, with the approval of the Steering Committee, set up a working group of interested individuals from the participating centers, including the NICHD Program Scientist and the DCC PI (or their designees), to assist with development of the protocol.

5.3.3 Full Protocols

The full protocol must convey a clear and complete account of how the study will be implemented. It should include all elements in the Protocol Checklist (see Appendix D):

- Section 1: Abstract. A brief summary of the proposed research, including primary hypothesis and research question.

- Section 2: Statement of problem. A description of condition under research, current practice, and gaps in knowledge.
- Section 3: Hypothesis. The specific question(s) (i.e., null hypothesis) that this study will answer.
- Section 4: Specific aims. The study's primary and secondary objectives (what will be evaluated, compared, or determined by the study results)
- Section 5: Rationale/justification. Describe any specific problems or challenges of the study and how these will be addressed
- Section 6: Background and significance. A review of work in this area, including relevant previous and ongoing in vitro, animal, and human studies
- Section 7: Methods and procedures
    - Study design (masked, randomized, etc.)
    - Study population
    - Inclusion and exclusion criteria
    - Enrollment Centers and PIs
    - Study intervention and procedures
    - Required follow-up (including whether FU needs to be blinded)
    - Primary and secondary outcomes (precise definitions related to study hypotheses)
    - Sample size estimate with statistical support based on primary outcome (including estimates of compliance and consent rates)
    - Available population and compatibility with ongoing NRN protocols
    - Projected recruitment time
    - Data analysis plan
    - Data safety monitoring plan, including required reporting procedures for serious adverse events and interim data analyses
    - Stopping limits for protocol termination
- Section 8: Budget. Detailed spreadsheets itemizing the elements of the capitation rate(s) (staff time, drug and other supply costs, subject incentives, etc.) and the overall study costs (including costs for pharmacy start-up, subcontracts for testing, specimen shipping, training, equipment, etc.) with estimated indirect rates. Budgets should cover any pilot studies, main trial, and follow-up costs not normally covered under another ongoing NRN protocol.
- Appendix A: Authorship plan.

PIs developing protocols are encouraged to consult previous protocols and to consult the DCC as they develop their protocols. When developing a protocol, the study PI should consider availability of the study population.

All protocols must be approved by the center PI prior to submission to the Protocol Review Subcommittee for review.

5.4 Protocol Review Process

5.4.1 Submission

Once a draft is completed, the study PI should forward it via email to the Protocol Review Subcommittee Chairperson and the NICHD Program Scientist.

Upon receipt of a draft protocol, the chair of the Protocol Review Subcommittee and the NICHD Program Scientist review it to ensure that all required elements are included.

5.4.2 Review Process

If the protocol has all the required elements, it is forwarded to the Protocol Review Subcommittee, and 2-3 subcommittee members are assigned to prepare formal written reviews of the protocol's design and feasibility (similar to the NIH scientific review process). When needed, non-subcommittee members may be solicited to review the draft protocol. Reviewers present their critiques, usually via teleconference, to the Protocol Review Subcommittee for further discussion and proposed recommendations. The subcommittee may request that the Study PI participate in a portion of this teleconference to answer any questions the reviewers may have. The subcommittee then votes on whether to approve the protocol as is, request revisions, or reject the protocol. Following the teleconference, the subcommittee chair drafts a summary of the reviews and discussion. Once approved by the subcommittee, the chair forwards this summary to the study PI. Reviews are generally completed within 2-3 months of protocol submission.

If the Study PI or the Study PI's sponsoring Center PI is also a member of the Protocol Review Subcommittee, he or she will recuse themselves from the review and voting process for their proposed protocol.

5.4.3 Revisions

If the subcommittee requests revisions, the study PI must revise and resubmit the protocol to the Protocol Review Subcommittee *within 6 months*.

5.5 Protocol Approval Process

5.5.1 Steering Committee Presentation

If the Protocol Review Subcommittee approves the protocol, the investigator can make final revisions and forward the draft protocol to the Steering Committee. The study PI will be asked to present the protocol at the next available Steering Committee meeting. Presentations should be no more than 20 minutes and will be followed by a 20-minute discussion session. The study PI should submit the revised protocol and any accompanying handouts to the NICHD Program Scientist *at least three weeks prior to the assigned Steering Committee meeting*, to allow sufficient time for Steering Committee members to review the materials.

5.5.2 Scientific Merit Vote

Following the meeting, each Steering Committee member presents the protocol to his/her center's faculty and staff for their concurrence and comments. The study PI may develop a PowerPoint presentation for use in these presentations. The NICHD Program Scientist compiles comments from the centers and forwards them to the study PI for responses and/or revisions.

The Center PI then sends his/her Steering Committee vote for Scientific Merit to the NICHD Program Scientist; votes are due within 4 weeks of the presentation to the Steering Committee. If ⅔rds of the Steering Committee votes to approve the draft protocol, it can advance to the Protocol Stage, and a formal protocol subcommittee is set up.

5.5.3 Advisory Board Approval

Once the Steering Committee approves a protocol's scientific merit, the NICHD Program Scientist forwards the protocol to the Advisory Board for its approval. The board votes on whether to proceed with the proposed study and makes a formal recommendation to NICHD. The Advisory Board can approve, request changes, or reject the protocol based on a simple majority vote.

5.5.4 External Review

At the same time that the NICHD Program Scientist forwards the protocol to the Advisory Board, he or she also sends it to 2-5 external experts for an outside review. The external reviewers, who generally remain anonymous, send their comments and suggestions back to NICHD. The NICHD Program Scientist forwards a summary of comments to the protocol subcommittee for responses and/or revisions.

5.5.5 Budget Priority Vote

After any revisions are made to the protocol, manual, forms, and budget (based on recommendations from the Advisory Board and external experts), the Steering Committee takes a final budget vote to prioritize/rank all draft protocols currently approved for implementation. The NICHD Program Scientist makes a final decision on which protocols can proceed with implementation based on this ranking and availability of funding.

5.5.6 Protocol Subcommittee Formation

Once approved for funding, an official Protocol Subcommittee is formed. See Section 3.5 for details on how subcommittee membership is determined. In general, the original author of the protocol is both the study PI and the chairperson of the protocol subcommittee; once formed, the subcommittee elects a vice chair. Once established, the protocol subcommittee is responsible for developing all protocol documents.

5.5.7 Develop the Protocol, Manual, and Forms

The protocol subcommittee is responsible for making any required revisions to the protocol, based on comments received during the review and approval processes. The subcommittee works with the Data Coordinating Center to develop a detailed protocol manual and data collection forms. The subcommittee then forwards the protocol documents to the Steering Committee for final input.

5.5.8 Data Safety Monitoring Committee Approval

Once the protocol subcommittee finalizes the protocol, the Data Coordinating Center forwards the documents to the DSMC for its review and approval. As per its Charter (Appendix B), new protocols are referred to the DSMC for their review and approval of the following aspects:

- The DSMC is requested to make a recommendation about the study's ability to answer the question at hand.
- The DSMC is requested to review the adequacy of the proposed interim monitoring plan and potential harms, if any from the study.
- If there are missing elements that impinge on the ability of the study to answer its stated questions and/or to adequately safeguard and monitor patient safety, the DSMC may recommend additions and modifications to the study.

The DSMC can approve, request changes, or reject the protocol based on a simple majority vote.

5.5.9 Investigational New Drugs

Trials involving investigational drugs usually require an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA). NICHD is the IND holder for NICHD-sponsored NRN protocols. The NICHD Program Scientist, with the assistance of the Study PI and the DCC, coordinates FDA requirements and correspondence on behalf of the Network.

5.6 Protocol Implementation

5.6.1 Implementation Planning

Following DSMC approval, planning begins for protocol implementation:

- The Study PI and research coordinators review the protocol, manual, and forms, looking at feasibility issues and preferred form and data entry formats
- The Study PI with the DCC finalizes the protocol, manual, and forms
- The research coordinators conduct a pilot test of the manual and forms
- DCC staff post the final documents on the private NRN website
- Centers apply for IRB approval
- DCC staff set up randomization systems (if needed) and program and transmit the data management system to sites for data entry

- The Study PI and DCC train and certify the research coordinators in protocol implementation, reviewing the forms and discussing: consent and recruitment issues, eligibility criteria, randomization process, implementation activities, use of required equipment or drugs, specimen or test result shipping procedures, pharmacy set up, and data entry procedures.
- Research coordinators train their local staff on the protocol
- The Study PI or his/her designee trains and certifies research specialists (ophthalmologists, surgeons, etc.), as needed
- DCC staff in conjunction with the study PI set up a system for coordination. procurement and distribution of any centrally-ordered equipment, study drugs, and supplies, as needed

During this process, questions or issues may arise that were not previously addressed in the approved protocol. The Protocol Subcommittee is responsible for considering and responding to these issues in detail. The subcommittee chairperson must report any major issues and make recommendations for any major protocol changes to the Steering Committee.

5.6.2 Recruitment Begins

Once the DCC IRB approves the protocol, the research coordinators are trained, any centrally-ordered equipment or supplies are distributed, and the data management system has been forwarded to sites, the DCC coordinator notifies centers that they can start recruiting subjects for the study, pending approval of each site's local IRB.

5.6.3 Protocol Supervision and Communications

The Protocol Subcommittee and DCC are responsible for supervising study implementation at the Network level, informing the Steering Committee of all major implementation issues.

As part of this process, the Protocol Subcommittee meets regularly to discuss protocol issues, including recruitment, implementation, proposed secondary studies, etc. The subcommittee chairperson presents a status report on the protocol at each face-to-face Steering Committee meeting. The study PI may also participate in Steering Committee teleconferences, at the request of the Steering Committee chairperson.

During protocol initiation and implementation, the study PI participates in the monthly Coordinators teleconference to update the research coordinators of any new changes and discussing any issues the coordinators may have encountered during implementation.

5.6.4 Adverse Event Reporting

Sites send MedWatch forms for adverse events to NICHD and the DCC. As per the protocol's data safety monitoring plan, the DCC PI notifies the chair of the DSMC, NICHD, and the FDA and/or other relevant regulatory agencies, in a timely manner, of any serious, unexpected, and related adverse events or apparent trends that may affect patient safety. The DSMC meets at regular intervals to review planned interim analyses. See Section 3.2 for details.

5.7 Secondary Protocols to Primary Studies

Secondary protocols are studies or trials designed to complement a primary protocol (Note: secondary analyses of primary study data are discussed separately under Section 5.9). A secondary protocol should not interfere with the objectives of the main trial. Because of this all proposed secondary studies must be submitted to the Protocol Subcommittee for the relevant main study. The Protocol Subcommittee evaluates the proposal for scientific merit and ensures that it will not adversely affect the primary trial's enrollment, implementation, or results.

Secondary studies for the Generic Database are discussed in Section 5.8.

5.7.1 Concept Proposals for Secondary Studies

The review process for secondary studies is similar to that of primary study protocols, except that the concept proposal is presented to the primary study's Protocol Subcommittee first; if the subcommittee approves it, and the budget is more than $20,000, then the concept will be presented to the Steering Committee. The concept proposal should follow the guidelines listed in Section 5.1.

The Study PI must submit a concept proposal to the Protocol Subcommittee chairperson, who will distribute it to the subcommittee members for review. The Study PI may be asked to present the concept on a subcommittee teleconference and/or at the next subcommittee meeting.

Following the presentation, if ⅔rds of the subcommittee members vote to approve the concept, it can advance to the next stage.

5.7.2 Secondary Studies Less than $20,000

A subcommittee-approved secondary study that is estimated to cost less than $20,000 total costs (direct + indirect costs) does not need additional approvals from the Protocol Review Subcommittee or Steering Committee. The Protocol Subcommittee chairperson notifies the Steering Committee about the approved secondary study as part of his/her regular reporting.

Once the subcommittee approves the study, the Secondary Study PI begins working with the DCC to develop a protocol, manual, and data forms (or modifying existing forms), as per Section 5.4.7.

When the protocol documents are completed, the NICHD Program Scientist and the DCC PI will determine, based on the proposed protocol activities, whether the Advisory Board or DSMC needs to review and approve the secondary study.

5.7.3 Secondary Studies More than $20,000

If the subcommittee-approved secondary study is estimated to cost more than $20,000 total costs, then the study proceeds through the normal Protocol Review and Approval processes, in the same way as a primary study protocol (see Sections 5.2, 5.3, and 5.4).

5.7.4 Secondary Study Subcommittees

In general, the primary study Protocol Subcommittee serves as the secondary study subcommittee. See Section 3.5 for details.

5.8 Ancillary Studies to Primary Studies

The NRN does not provide support for data collection or analysis for ancillary studies. The investigator must provide funding to cover any additional effort (research time, supplies, statistical analysis, etc.) required to conduct the study. Any ancillary study of subjects enrolled in a NRN study or trial must be done under the supervision of a NRN Center PI.

Ancillary studies involving multiple centers may require significant input from the DCC to ensure scientific integrity. In such cases, the studies should be proposed as secondary protocols, subject to the approval process described in Section 5.7, Secondary Protocols to Primary Studies.

The relevant Protocol Subcommittee(s) or the Steering Committee should review all ancillary study manuscripts prior to journal submission. Requests for restricted access to study results – for example, for the analysis of ancillary studies performed at individual centers – are not honored if it might lead to premature disclosure of the results of the primary study.

5.9 Generic Database and Follow-up Study Revisions and Additions

The core Generic Database is a limited dataset that represents important and essential information about preterm infants – data that could show changing trends over time, based on changes in medical practice and other factors. Similarly, the Follow-up (FU) Study consists of data representing important and essential information about the development of preterm infants. As knowledge and practice changes, in terms of medical treatment, knowledge of development, and new developmental testing materials, it is necessary to change the core data collected for the GDB and/or FU Study – making additions, deletions, or revisions of the data points collected – from time to time.

All proposed changes to the GDB and FU must undergo a thorough, formal review to determine whether the proposed changes are appropriate and acceptable, and whether they should be permanent or time-limited in duration. Permanent changes to the core GDB or FU will be considered in the second year of each 5-year grant cycle. Special exceptions to change the data collection core may be made outside of this timeframe with the approval of the Steering Committee.

PIs may send formal requests to revise, add to, or delete items permanently from the GDB or FU core data to the Protocol Subcommittee chair, who will distribute it to the subcommittee members for review. The Study PI may be asked to present the request on a subcommittee teleconference and/or at the next subcommittee meeting. Following the presentation, if ⅔rds of the subcommittee members vote to approve the request, the proposal will be presented to the Steering Committee as a concept. If the Steering Committee approves it, then the Study PI will work with the relevant subcommittee to develop new forms and/or modify existing forms and to revise the manual and protocol as needed.

The core GDB and FU data are not intended to include detailed data on areas of special interest in this population. Such data, in sufficient detail to provide meaningful information, can be collected as an addendum to the core GDB or FU after appropriate approval. Study PIs may submit concepts for secondary protocols for time-limited detailed data collection to the GDB Subcommittee or Follow-up Protocol Subcommittee chairperson. Such proposals will be processed in the same manner as other secondary protocols, per Section 5.7, Secondary Protocols to Primary Studies.

5.10 Secondary Analyses of GDB, FU, and Study Data

Study PIs can submit concepts for secondary analyses of NRN data from completed primary or secondary studies, or from the GDB or FU. Study PIs should submit concepts to the relevant Protocol Subcommittee(s) for review and approval. See Section 6.2, Abstract Review Process, for details on timelines and procedures.

Chapter

6

Publications

The goals of the NRN Publication policies are to:

- Encourage the timely preparation of high quality publications and presentations from NICHD Neonatal Research Network (NRN) studies.
- Provide appropriate academic recognition to participants who make significant and substantial contributions to NICHD Neonatal Research Network studies.

All NRN manuscripts and abstracts, except for ancillary studies, must be submitted to the Publications Subcommittee for review and for NICHD clearance prior to journal/meeting submission. Ancillary study manuscripts should be reviewed by the relevant Protocol Subcommittee(s) or the Steering Committee prior to journal submission.

6.1 Definitions

Interview – An interview is any discussion with a member of the formal or informal news media that provides information for public dissemination.

Presentations -- A presentation is the delivery of information to scientific, professional, or public groups, such that public dissemination might ensue through publication, press releases, etc. A seminar given within a closed academic setting is not considered a presentation.

Press release -- A press release is defined as a document given to radio, television, newspapers, and popular periodicals without national circulation or scientific journals not indexed in Index Medicus.

Publication – A publication is any document submitted to a professional journal listed in Index Medicus or any popular periodical with national circulation. All publications of major results of a trial will be prepared under the direction of the protocol subcommittee. Publication of results of ancillary studies by individual investigators will be allowed with approval by the Steering Committee.

6.2 Timetables and prioritization

To facilitate and maximize the productivity of the Network, the following guidelines will be used concerning data analysis and write-up of protocol results. Timelines for abstracts are included in Section 6.3.1.

6.2.1 Timetable for Publication of Primary and Secondary Protocols

The Steering Committee expects that the results of all NRN primary studies will be submitted for publication within six months of study completion.

To publish primary study results in a timely manner, the NRN follows this timeline:

- The first author of a primary study should complete a first draft of the manuscript within three months of study completion – e.g., after the last subject has completed the primary study's activities and all relevant data has been collected and is available for analysis (e.g., three months after hospital discharge or follow-up of the last subject enrolled). To accomplish this, a "skeleton" of the paper with mock tables and figures can be put together by the subcommittee beforehand and various components of the manuscript will be assigned to the members of the subcommittee.
- Subcommittee members and other coauthors should review the draft and make recommendations for revisions within one month of completion of a first draft.
- Within a month of receiving comments, the first author should submit the revised draft to the Publications Subcommittee for review, per Section 6.5 below.

Secondary protocols should follow a similar timetable; however, secondary protocols typically cannot be submitted for publication until after the primary study paper has been accepted for publication.

6.2.2 Timetable for Secondary Analyses of Primary Protocols

Protocol subcommittee members are encouraged to submit requests for secondary analysis of the primary and secondary protocol data. Requests should explore specific hypotheses, preferably submitted before the investigators see the study data.

Subcommittee members can submit requests for secondary data analyses up to three months after the primary study manuscript has been submitted for publication. Thereafter, the Steering Committee members are given the opportunity to request data analyses.

If a large number of requests are submitted and approved, the subcommittee will prioritize the requests and submit the prioritized list to the Data Coordinating Center PI.

6.2.3 Prioritizing Data Analysis Requests

All data analysis requests must be approved by the relevant Protocol Subcommittee(s) and, for abstracts, the Abstract Review Subcommittee. Requests with specific deadlines (e.g., analyses for conference abstracts) must be submitted in a timely manner to give the Data Coordinating Center sufficient time to process them.

Because the DCC processes a fairly large number of new and ongoing data analysis requests, the NRN prioritizes which types of requests get processed first, using the following prioritization guidelines, with item #1 having the highest priority and #5 the lowest priority:

1. Primary protocols
2. Secondary protocols
3. Generic Database annual report
4. Secondary analyses of primary protocol data
5. Secondary analyses of GDB/FU data

Data analyses for manuscripts are generally given priority over those for abstracts. During October and November of each year, PAS abstract analyses take priority over pre-existing requests (manuscripts, pending presentations for other meetings, etc.), with the exception of primary protocol manuscripts and/or abstracts.

The above list is a guideline for general NRN practices – if a timely and exciting topic comes up that requires data analysis, a particular request may be given higher priority at the discretion of the DCC PI and the NICHD Program Scientist.

6.2.4 Timetable for Manuscript Review

Reviewers and the Steering Committee are given two weeks to submit their comments to the Publications Subcommittee chair.

The NICHD clearance process generally takes two weeks to complete.

6.3 Abstract review process

Study PIs should submit concepts for abstracts and secondary analyses to the relevant Protocol Subcommittee(s), the NICHD Program Scientist, and the DCC PI, per the timeline below. Requests must be submitted in sufficient time so that they do not compete with the ongoing NRN research or analysis of NRN primary or secondary studies.

Submitting an abstract implies a commitment on the part of the Study PI to draft and submit a manuscript for publication. Because of this, abstract proposals require the approval of the appropriate subcommittee(s). *An Investigator who has an outstanding abstract – one for which*

he/she has not submitted a draft manuscript to the Publications Subcommittee for review – will not be allowed to submit additional proposals for abstracts or manuscripts.

6.3.1 Timeline for Meeting Abstracts

The DCC PI and NICHD Program Scientist issue specific abstract development timelines with deadlines for large research meetings, such as for the Pediatric Academic Societies annual meeting. The timeline outlines deadlines for:

- Submission of abstract proposals to the Abstract Review and relevant Protocol Subcommittees (~6 months before the meeting deadline)
- Review of abstract proposals
- Submission of draft abstracts to the Publications Subcommittee for review and the NICHD Program Scientist for NICHD clearance (usually one month before the meeting abstract deadline)
- Approving draft abstracts
- Submission of abstracts to the meeting
- Submission of final conference materials (presentation slides, posters, etc.) to the NICHD Program Scientist for NICHD clearance (3 weeks prior to the meeting)

6.3.2 Abstract Proposals

Abstract proposals should follow the guidelines of the Protocol Review Checklist (see Appendix D). Study PIs should review the current NRN Publications list (available on the NRN website: neonatal.rti.org) to ensure that the proposed abstract does not overlap with any previous abstracts and/or publications.

Abstract proposals should be submitted before the pre-approved deadline to the NICHD Program Scientist who will distribute them to the Abstract Review Subcommittee and relevant Protocol Subcommittee(s) for comment.

The Abstract Review Subcommittee and relevant Protocol Subcommittees will meet, either in person or via teleconference, to review the abstract proposals. The protocol subcommittees may approve, disapprove, or request clarifications or revisions for proposed analyses. Once the subcommittees have reviewed all of the proposals, the Abstract Review Subcommittee will prioritize them.

6.3.3 Submission of Draft Abstracts to the Publications Subcommittee

Once an abstract is accepted to move forward, the first author should contact the RTI statistician assigned by the DCC PI as soon as possible. Authors of approved abstract proposals should collaborate with the DCC and Protocol Subcommittee members to analyze the data and draft the abstract. See Timetables, Section 6.1, for guidelines for how data analysis requests are prioritized.

Once finalized, the first author must submit the abstract to the Publications Subcommittee for review and approval, and to the NICHD Program Scientist for NICHD clearance. All abstracts must be submitted for NICHD clearance at least two weeks prior to the meeting submission deadline.

Once approved by the Publications Subcommittee, the abstract may be submitted to the meeting organizers for consideration.

6.3.4 Draft Presentation Materials

Following acceptance of an abstract, the author(s) will work to develop necessary meeting presentation materials (posters, presentation slides, etc.). The first author must submit the draft presentation materials to the Publications Subcommittee and NICHD Program Scientist at least one month prior to the date of the presentation. The Publications Subcommittee will review the materials and recommend modification to improve the quality of the presentation and ensure that the abstract will result in a journal submission.

All presentations must be submitted for NICHD clearance at least 3 weeks prior to the date of the presentation.

6.4 Public Presentations of NRN Protocol Results

6.4.1 Public Relations and Presentations Prior to Publication

During the protocol implementation and prior to formal publication and/or presentation of a NRN primary protocol's results, the Steering Committee, via the NICHD Program Scientist, will ideally respond to all inquiries from the lay or scientific press. As part of this, the NICHD Program Scientist will coordinate, monitor, and review press releases, interviews, presentations, and other public relation opportunities.

Should a NRN center be solicited for information other than that detailed above, the center should refer the soliciting party to the NICHD Project Scientist. The Steering Committee must approve any pre-publication discussion of a NRN protocol that extends beyond these items of information. Guidelines for initiation and review of such presentations are the same as those for publications.

For descriptive presentations, the PI should inform the NICHD Project Scientist ahead of time, and forward the presentation materials to the DCC PI for his/her review and approval.

6.4.2 Confidentiality of Protocol Results

When the primary outcome data is presented to the Steering Committee, the information shall be kept confidential within the Steering Committee until an abstract is published or presented at a regional or national peer reviewed society meeting, or until a manuscript is published in a peer-reviewed journal, whichever comes first. The results may be shared with colleagues within NRN

Centers after they are made available to the Steering Committee; however, the Center PIs should caution their colleagues to protect the confidentiality of the data.

The data derived from NRN randomized controlled trials or observational studies may be released after the publication of primary manuscripts. Manuscripts based exclusively on the Generic Database or Follow-Up Study are excluded from this policy as these studies are longitudinal projects.

6.4.3 Presentation and Publication of Results

Primary outcome data, particularly those involving intervention studies, should be presented first in a national or regional peer review forum, such as the Pediatric Academic Societies annual meeting. If the forum is somewhere other than the PAS meeting, the Steering Committee will vote on approval of the presentation venue.

6.4.4 Public Relations Regarding Results

When a protocol's results are published or formally presented, the NICHD Program Scientist will determine -- in consultation with the Study PI, the DCC PI, and NICHD Public Information and Communications Branch – whether the findings may require a formal NICHD press release. This is usually reserved for high-profile and/or high-impact results. If the results meet these criteria, the Program Scientist will work with the NICHD Public Information and Communications Branch to develop a public relations strategy, which may include drafting a press release, developing NRN talking points for media interviews, etc. Sites are encouraged to contact the NICHD Program Scientist to discuss potential press releases and press conferences.

6.4.5 Public Relations and Presentations after Publication of Results

Following this peer-reviewed presentation or publication in a peer-reviewed journal, the data can be presented in public forums.

6.5 Manuscript review process

All NRN manuscripts, except ancillary studies, must be submitted to the Publications Subcommittee for review. The Publications Subcommittee must review and approve all manuscripts prior to submission to journals or societies for publication or presentations. See Figure 2, the Publications Process flowchart, on the next page for an overview.

Ancillary studies should be sent to the NICHD Program Scientist when submitted for publication or presentation, and the first author should forward a final copy of the manuscript to the NICHD Program Scientist.

6.5.1 Draft Stage

The first author is responsible for producing a first draft of a manuscript, working with the designated DCC statistician and collaborating with any coauthors. The first author should format the manuscript in accordance with the specific directions for the journal to which he/she will submit it.

Once the first author drafts a manuscript, all coauthors must review both the manuscript's content and format and approve it. The first author is responsible for incorporating comments and recommendations at each stage of the Publication Process. All authors must complete the NRN Authorship Responsibility Form (available on the NRN private website).

Once all authors have reviewed and approved the manuscript, the first author should submit the revised manuscript to the relevant Protocol Subcommittee(s) for review and approval.

6.5.2 Acknowledgements Boilerplate

The first author should send a copy of the draft manuscript to the NICHD Network Coordinator and a request an acknowledgements boilerplate and review of the proposed author list. The NICHD Network Coordinator will draft a boilerplate in accordance with Section 6.7 and review the author list and affiliation. He/she will send the boilerplate to the relevant PIs for review and approval, and forward the final boilerplate to the first author for incorporation into the manuscript.

6.5.3 Review Stage

Once all authors and the relevant subcommittee(s) have reviewed, given their input, and approved the manuscript, and the first author has addressed any concerns raised, the first author must send the manuscript and the completed Authorship Forms to the Publications Subcommittee chairperson. The manuscript should be a final draft of peer-review quality. The chairperson will forward the manuscript to reviewers within the NRN; he/she will also forward it concurrently to the Steering Committee and PIs from former NRN sites that contributed data to the manuscript as a courtesy for their review and approval.

The Publications Subcommittee chair assigns the manuscript to at least two NRN PIs or their designees for review; if the Publication Subcommittee chair is an author on the paper, or otherwise in conflict, the vice-chair will manage the review process. If the manuscript is derived from the GDB or Follow-Up Studies, the chair will assign at least one member from the relevant subcommittee(s) as a reviewer. Other reviewers may be invited to review manuscripts based on their expertise at the discretion of Publications Subcommittee chairperson and the NICHD Program Scientist.

Reviewers are given two weeks to submit their comments to the Publications Subcommittee chair, who compiles and distributes them to the first author.

6.5.4 NICHD Clearance

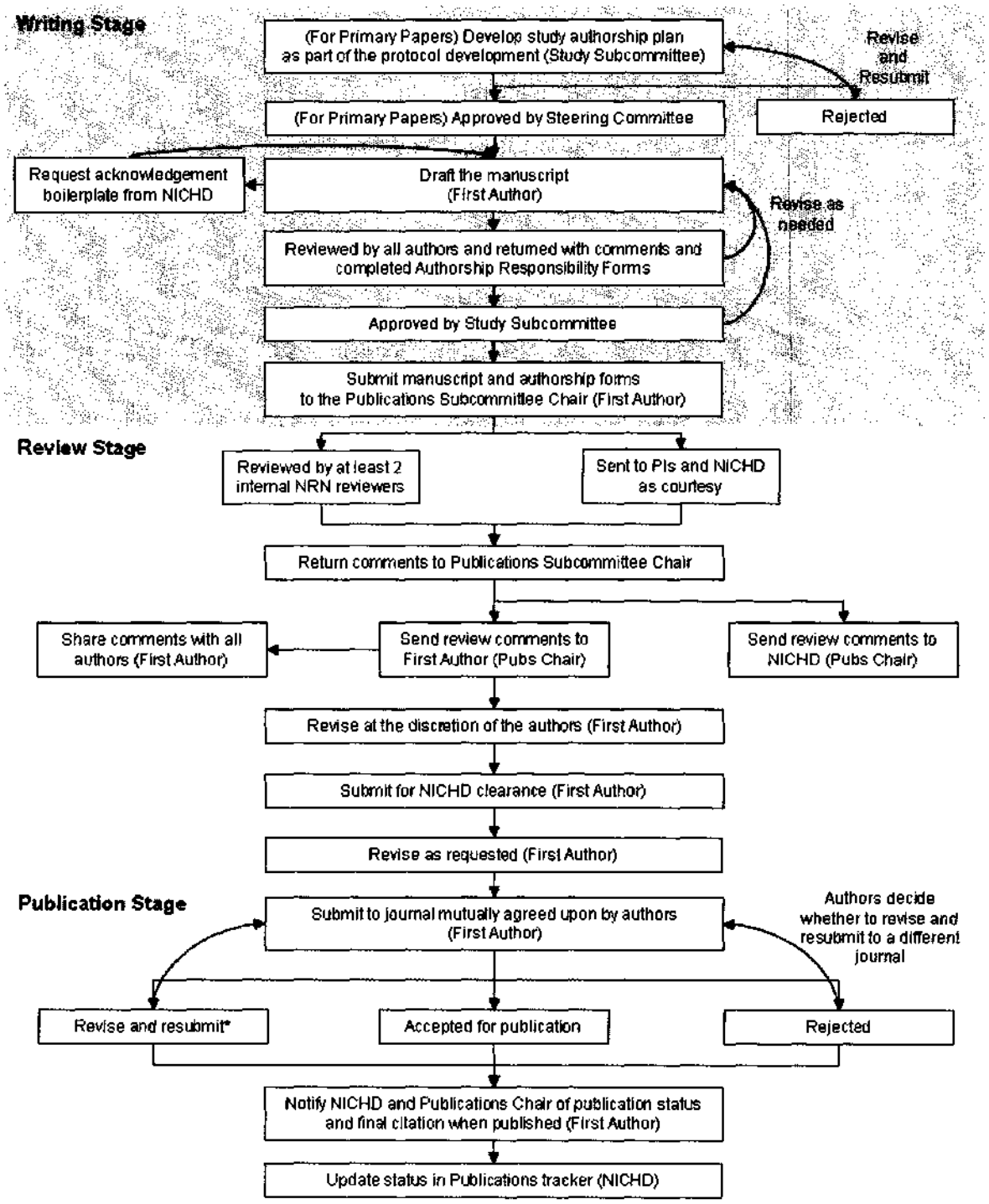
All NRN publications must be submitted for NICHD clearance by the NICHD Project Scientist or his/her designee. Once the first author incorporates the comments and suggestions of the Publications Subcommittee and Steering Committee, he/she must send the revised manuscript to the NICHD Program Scientist to go through the NICHD clearance process.

Studies that involve other sponsors (e.g., other NIH Institutes, CDC, etc.) may need to go through additional clearance process(es) through the sponsors.

6.5.5 Publication stage

The first author is responsible for managing the manuscript submission process, gathering all required forms (copyright authorization forms, conflict of interest forms, etc.) from coauthors and submitting them, as required by the journal.

Neonatal Research Network Publications Process



* Note: Major revisions may require re-review, subcommittee approval, and/or NICHD clearance.

The first author is responsible for making revisions, correcting proofs, and resubmitting to different journals, as needed. He/she should keep the NICHD Program Scientist and Network Coordinator informed of the submission status (submitted, revisions requested/submitted, accepted/rejected, resubmitted to a different journal, etc.), and forward them a copy of the published manuscript.

Once published, the first author is responsible for complying with the NIH Public Access Policy. See Section 6.8 for details.

6.5.6 Publications tracking

The Publications Subcommittee chair, with the assistance of the NICHD Coordinator, is responsible for tracking NRN publications. The Publications tracker includes both published articles and unpublished active, upcoming, and withdrawn items.

The tracker will be updated prior to every Steering Committee meeting. To do this, the NICHD Network Coordinator will request status updates on all active items, coping both the first author and his/her center PI. If no response is received in more than 12 months after repeated contact attempts, the first author and his/her PI will be notified that the item will be automatically withdrawn.

6.6 Authorship

NRN Authorship policies vary by protocol type (primary, secondary, pilot, special, and ancillary protocols and secondary analyses). Authorship plans should be developed as part of the protocol.

6.6.1 Abstracts

For abstracts of primary protocols, the Protocol Subcommittee chair will be the author followed by "for the NICHD Neonatal Research Network." For other abstracts, if the first author is a fellow/junior faculty, a senior investigator may be listed. Occasionally, more than one author may be listed on behalf of the NICHD Neonatal Research Network, depending on available space. Additional authors must be approved in advance by the Protocol Subcommittee.

Note that abstract authorship does not determine authorship on the final manuscript.

6.6.1 Primary Protocols

Preferred Method of Determining Authorship
If a journal does not have a limit on the number of authors that may be included on a paper, all participants meeting the journal's authorship requirements are listed in the following order:

1. The first author is the Protocol Subcommittee chairperson

2. Remaining members of the protocol subcommittee. At the time the abstract or manuscript is prepared, the first author will make recommendations on the author order – taking into consideration member efforts during protocol development, protocol drafting, meeting participation, performance monitoring, data analysis and interpretation, and abstract and/or manuscript preparation – for Protocol Subcommittee approval.

3. The study statistician(s) (identified by the DCC PI)

4. Remaining participating Center PIs (those not serving on the Protocol Subcommittee), listed in order by the Center's combined ranking of the number of infants enrolled and the percent of eligible infants enrolled in the study by the Center. Table 6.6.1 illustrates how to calculate the order. The PI for each Center will determine who from their center will be listed.

5. Followed by the phrase "for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network"

Table 6.6.1. Authorship Ranking

Center	Ranking Based on Number Enrolled	Ranking Based on % Eligible Infants Enrolled	Total Score	Authorship Ranking
A	1	3	4	1
B	2	2	4	2
C	3	1	4	3
D	4	5	9	5
E	5	6	11	6
F	6	2	8	4

Change of Principal Investigator

Network participants may change during any particular study, for the purposes of authorship, the Principal Investigator identified at the time of study approval will ordinarily remain the PI listed on the paper. However, if the Steering Committee chairperson and the NICHD Project Scientist determine that that individual was unable to continue to participate in the study, the principal authorship will go to the individual from the subcommittee who has been most active in the study. The original Principal Investigator will receive authorship if he/she participates significantly in the design, conduct, analysis, and publication of the trial.

More than one author from a participating center or the DCC

A Center PI may nominate a second author from his/her center, who has provided special expertise and/or made other significant contributions to the protocol. The Protocol Subcommittee will vote on whether to approve the addition; if the subcommittee approves it, the Steering Committee will then vote on whether to approve the addition. If the Steering Committee approves the inclusion of two authors from the same Center, the Center PI will decide who will be listed first from that center. If the Steering Committee rejects the nomination, the Center PI will determine who will be the single author from that center.

Additional authors
On a case-by-case basis, the Protocol Subcommittee can propose that additional authors be included. The Steering Committee will vote on whether to approve the subcommittee's authorship plan. An authorship plan should be developed concurrently with the protocol as soon as it is recognized that additional expertise is required to bring the project to fruition.

Alternate Method of Determining Authorship
If a journal limits the number of authors that may be included lower than the number of authors that would be listed under the Preferred Method, authors will be included in the following order:

1. The first author is the Protocol Subcommittee chairperson

2. Remaining members of the protocol subcommittee. At the time the abstract or manuscript is prepared, the first author will make recommendations to the Protocol Subcommittee on the author order – taking into consideration member efforts during protocol development, drafting, meeting participation, performance monitoring, data analysis and interpretation, and abstract and/or manuscript preparation. The subcommittee will approve the order.

3. Principal study statistician (identified by the DCC PI)

4. Followed by the phrase "for the NICHD Neonatal Research Network"

The names of the NRN authors who could not be listed on the title page will be listed as authors in an acknowledgement section.

6.6.2 Secondary Protocols

The protocol subcommittee, with Steering Committee approval, determines the authorship of secondary protocol papers.

6.6.3 GDB Papers

For predefined secondary studies, such as time-limited addition to the Generic Database, GDB Subcommittee members are listed as authors.

For post-study secondary analyses, the abstract proposal and paper go through the subcommittee for review. Authorship is determined at that point in time.

The paper's first author should recommend authorship order – taking into consideration member efforts during conceptual input, protocol drafting, meeting participation, performance monitoring (if relevant), data analysis and interpretation, and abstract and/or manuscript preparation – for subcommittee approval at the time the abstract or manuscript is being prepared.

6.6.4 Pilot protocols

Pilot data may be published as a separate manuscript, with the PI of the pilot protocol as the first author. The authors ordinarily include the members of the Protocol Subcommittee for the planned primary protocol, the study statistician, and the PIs of the Centers that participated in the pilot study, following the guidance in Section 6.6.1 for primary protocols.

6.6.5 Special protocols

Authorship for special protocols follows the guidelines or policies of the primary sponsor of the project, and should be consistent with any legal agreement of participating agencies or organizations.

6.6.6 Ancillary Protocols

The Ancillary Study PI and the Center PI determine the authorship of ancillary studies papers.

6.7 Acknowledgements

All studies will acknowledge the support of the NICHD Neonatal Research Network at the foot of the title page as: "This work was supported in part by grants from the NICHD Neonatal Research Network," and will list all relevant grant numbers. If additional institutes or agencies co-fund a specific project, acknowledgements should also include this support.

Each manuscript will acknowledge efforts of the NRN research staff – from participating Centers, the Data Coordinating Center, NICHD, and other participating organizations – that helped with protocol development, study implementation (for main study and follow-up), specimen and data analyses, and/or manuscript preparation, and who are not already listed as authors on the paper. This may include:

- Steering Committee chairperson
- Principal investigators
- Alternate PIs
- Follow-up PIs
- Research coordinators
- Follow-up coordinators
- Follow-up examiners
- DCC coordinators and data managers

The PI of each institution is responsible for identifying the appropriate personnel to include in the acknowledgement boilerplate. Manuscripts involving follow-up examinations should include the participating centers' Follow-Up personnel. Staff who participated at study sites during specific protocols should be listed in the boilerplate.

Once a manuscript is nearly finalized, the first author should send a request to the NICHD Network Coordinator for an acknowledgement boilerplate. The NICHD Network Coordinator compiles a draft boilerplate for the paper and forwards it to the PIs of the participating centers for their review and concurrence. Once all PIs have responded, the Network Coordinator forwards the final boilerplate to the first author for incorporation in the paper.

6.8 NIH Public Access Policy

As part of the Congressional "Consolidated Appropriations Act" for 2008, effective as of April 7, 2008, all NIH investigators must submit their publications to the PubMed Central database, via the NIH Manuscript Submission (NIHMS) system, within 12 months after publication. The main reason for this is to give taxpayers free access to the results of the research that they are funding.

The official policy (publicaccess.nih.gov/policy.htm) states that:

> The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: Provided, that the NIH shall implement the public access policy in a manner consistent with copyright law.

Note: PubMed Central (www.pubmedcentral.nih.gov) is a separate database than PubMed.

For the NRN, the first author is responsible for ensuring that:

- The NRN paper and all supplemental materials are submitted on time
- All relevant authors and grant numbers are properly listed

Once the paper has been submitted, the first author should notify the NICHD Network Coordinator of this and/or send him/her the NIHMS ID number for the Publications Tracker.

Appendix

A

Network Members (2006 - 2011)

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Brown University

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Roger G. Faix, MD
University of Utah

Seetha Shankaran, MD
Wayne State University

Richard A. Ehrenkranz, MD
Yale University

Appendix

B

Data Safety and Monitoring Committee Charter

The *Eunice Kennedy Shriver*
National Institute of Child Health and Human Development (NICHD)

Official Charter of the
Data Safety and Monitoring Committee (DSMC) for the
Neonatal Research Network

January 1, 2010

Charter for the Data Safety and Monitoring Committee for the
Neonatal Research Network

1. Introduction

This Charter is for the Data Safety and Monitoring Committee (DSMC) for the *Neonatal Research Network (NRN).* This Charter will be reviewed every 3 years by the DSMC to determine whether any changes in procedure are needed. All version updates to this document are tracked in the table below.

Details of Change	Date Change was Finalized
Drafted Charter	7/2009

Each member of this DSMC must agree to the terms outlined in this charter. Each member will sign the *Acceptance of DSMC Terms and Conditions Form* to illustrate this agreement. Once this charter is finalized, it is to be reviewed in a DSMC meeting, signed by all members, and the signed copies will be provided to the NICHD Executive Secretary to the DSMC.

2. Purpose and Responsibilities of the DSMC

1. The members of the DSMC identified in this Charter for the *Neonatal Research Network* are responsible for safeguarding the interests of study participants and assessing safety. This includes ensuring and enhancing the safety of the study; that is, to protect the study participant from unacceptable risk.

2. The DSMC assesses the efficacy of *Neonatal Research Network* study protocols involving high risk procedures or interventions. Prior to DSMC review of the protocol in advance of study initiation, the NRN protocols go through multiple layers of rigorous internal and external review. An idea for a protocol is first presented as a concept to the NRN Steering Committee. If 2/3's majority vote is received, a protocol is developed and reviewed by the NRN Protocol Review Subcommittee. If the subcommittee approves the study, it is forwarded to the steering committee for a scientific vote. If the protocol receives 2/3 or greater majority for approval, it has passed the scientific vote. The protocol then undergoes advisory board and outside expert review. Concurrently, a protocol subcommittee is formed to revise and finalize the study based on steering committee comments, advisory board and outside review comments. If approved by a simple majority of the advisory board, the protocol goes for a budget vote to the Steering Committee. Once the protocol is finalized, it is referred to the DSMC for their review and approval of the following aspects:
   a. The DSMC is requested to make a recommendation about the study's ability to answer the question at hand.
   b. The DSMC is requested to review the adequacy of the proposed interim monitoring plan and potential harms, if any from the study. The DSMC may recommend mock data elements

(variables collected that are relevant to assessing safety, efficacy and matched recruitment during the study) for review as the protocol progresses with recruitment.

c. If there are missing elements that impinge on the ability of the study to answer its stated questions and/or to adequately safeguard and monitor patient safety, the DSMC may recommend additions and modifications to the study.

3. This Committee will serve as an independent advisory group to the Director of NICHD, and is required to provide recommendations to the Director of NICHD about starting, continuing, and stopping randomized clinical trials in the *Neonatal Research Network*. The general guiding philosophy for DSMC decision making with respect to ongoing studies is briefly described below.

3. DSMC Guiding Philosophy for Interim Monitoring

The DSMC will make decisions based on pre-specified guidelines included in the protocols for all NRN intervention studies. While the specific guidelines will be tailored to the safety and monitoring needs of each protocol, certain general principles are outlined here. Decision-making will explicitly include consideration of both statistical and non-statistical issues.

Stopping Rules for Safety

There will be explicit stopping rules for safety specified in the protocols for all intervention studies conducted by the NRN. The DSMC will review and agree to these rules (after any necessary modifications) as part of their initial review of a new study protocol. The principles of safety monitoring include the following:

- To ensure the safety of participants, safety will be monitored more frequently than efficacy.
- Statistical bounds for detecting group differences in safety events will be more liberal than those for efficacy

Typically, stopping rules for safety will involve looking at death and/or other pre-specified safety outcomes (frequently, a composite of any of these events) after the accrual of a fixed number of subjects into the study. This number will depend on the total sample size for a study, but will generally be small for potentially high risk studies involving interventions with little prior safety data. To ensure liberal bounds for stopping due to safety concerns, Pocock bounds will typically be used for monitoring safety.

Stopping Rules for Efficacy

There will be explicit stopping rules for efficacy specified in the protocols for all intervention studies conducted by the NRN. The DSMC will review and agree to these rules (after any necessary modifications) as part of their initial review of a new study protocol. The principles of efficacy monitoring include the following:

- The efficacy monitoring regime will be more conservative than that for safety because the emphasis here is on obtaining convincing evidence of treatment effects that are rarely apparent early on in a study.

- In order to avoid inflation of Type I error, require very strong evidence of a treatment effect for the study to terminate at the first interim look, whereas the criteria at the end of the study should be close to the nominal Type I error assumed for that study
- Use an alpha spending functions approach to adjust sequential monitoring bounds to account for any unequally spaced interim analyses (where outcomes cannot be obtained at pre-specified fixed points in time)

Typically, stopping rules for efficacy will involve looking at the primary outcome of the study at 3 or 4 interim points of data accrual. To ensure conservative bounds for stopping due to efficacy, O'Brien Fleming bounds will typically be used for monitoring efficacy (along with a Lan DeMets spending function for any unequally spaced interim analyses).

Monitoring of Bayesian trials

Interventions studies designed using Bayesian principles will apply some of the same principles stated above, but using a Bayesian framework. For monitoring safety, we will examine the posterior probability that one group has higher incidence of safety events than another. In statistical terms, the treatment will be considered harmful (i.e., the DSMC may consider termination of the trial) if for a pre-specified threshold η, the posterior probability of treatment harm (in terms of pre-specified safety events) is greater than η. We will similarly monitor the posterior probability of benefit that one group has lower incidence of the primary outcome than another, using a pre-specified threshold.

Since the choice of a prior distribution may be controversial in Bayesian analyses, these posterior probabilities will be obtained under two sets of priors – (a) a non-informative prior that does not assume any substantive prior information about treatment differences, and (b) an informative prior based on treatment differences observed in similar prior studies, if available.

Additional Considerations in Interpreting the Data

In addition to the statistical procedures described above, other considerations will be taken into account in interpreting interim results. It is important for these additional considerations to be stated in the study protocol to assure both study participants and investigators, who are masked to the data that the DSMC will carefully consider many issues related to safety and efficacy and will recommend protocol changes or study termination if warranted. Three important additional considerations will be (1) the consistency of the observed differences between treatment groups in variables that should be associated with one another, (2) the importance of these differences to the health and the safety of individuals in the trial, and (3) (if available) comparison of event rates in the study to historic rates observed in the NRN in a similarly defined population. Since the NRN has access to a rich database of events and outcomes for extremely premature babies over the last twenty years, these rates and their distribution across the different NRN centers can provide important perspective to DSMC deliberations.

Any differences between treatment groups in either outcome variables or adverse events will be considered for both their statistical significance and clinical importance. These considerations for interpretation of data require the combined expertise of clinical and statistical experts. A number of specific considerations for interpretation of these data can be stated in advance:

- Whether the magnitude or character of an observed difference constitutes a clinically important benefit or risk;
- Whether the risk under consideration is outweighed by assessment of the overall potential benefit of therapy;
- Whether the results could be explained by possible differences in baseline variables between the groups;
- Whether results could be due to ascertainment bias caused by differences in treatment regimens;
- Whether the results are consistent with those for other variables that should be associated with the variable in question;
- Whether the results are consistent among various subgroups of participants and across the various centers involved in the study;
- Whether it is likely that the current trends in the data could be reversed if the trial were to be continued unmodified;
- The degree of additional precision or certainty in the results that could be obtained by continuing the trial; and,
- Whether there would be significant loss in external validity or credibility of the trial by a change in Protocol or discontinuation.

In summary, a recommendation to modify or discontinue the trial would not be based solely on statistical grounds. Rather, it will be the result of well-reasoned consideration of all aspects of the data, with input from all members of the DSMC.

4. DSMC Members, Organizational Chart, & Communications

Members

DSMC Members include a panel of scientific experts with a designated chair and vice chair of the committee. In addition, ad hoc DSMC members may be selected for specific protocols. The DSMC members have voting rights whereas the ad hoc DSMC members only have voting rights for those protocols for which they advise upon. All members are appointed by the Director of the NICHD.

The chair of the DSMC acts as a default medical monitor for all trials. The vice chair serves as medical monitor if the chair is unavailable.

In addition, this DSMC has an Executive Secretary (ES) as a liaison to NICHD. The ES is responsible, in collaboration with the Data Coordinating Center (DCC), for assuring the accuracy and timely transmission of the final recommendations and DSMC minutes to the NICHD. .The ES is an ex-officio non-voting member of the DSMC.

The PI of the NRN DCC is an ex-officio non-voting member of the DSMC.

A list of all current voting and non-voting members of the DSMC (as of the date of this Charter) is provided in Appendix 1.

The DSMC will ideally meet in person at least once every year. Additional meetings will be scheduled based on protocol needs and adverse events.

Only members for this DSMC, and the DCC may attend closed sessions for this Committee. In addition, *only* DSMC members and the DCC will have access to privileged communications and discussions of this Committee. At its choosing, the DSMC can also meet in closed executive session without DCC staff present.

Communication
Communication with members for this DSMC will be primarily through the DCC. Investigators from the *Neonatal Research Network* will not communicate directly with DSMC members about the study, except when making presentations or responding to questions at DSMC meetings or during scheduled conference calls.

5. Conflict of Interest and Compensation

It is extremely important that all voting members of the DSMC state any real or apparent conflicts of interests at the onset of the study. Members of the DSMC shall read the NICHD Clinical Research Guidance Document regarding Conflict of Interest (COI) and provide their signed summary of any COI to the Executive Secretary or NICHD NRN Program Specialist for the study, when first appointed.

Prior to the review of new protocols by the DSMC as well as on a yearly basis, the DCC will solicit a COI declaration from each member to insure that real or apparent conflicts are disclosed and documented.

If a new conflict arises with a member, that is to be disclosed in a timely manner (within 30 days) to the DCC PI. If such a new conflict is reported, the NICHD will determine if the conflict limits the ability of the DSMC member to participate in the discussion.

All DSMC members will be compensated for their role in supporting the committee. Compensation will be per the guideline of *the Neonatal Research Network*. Current compensation involves travel, lodging if needed, per diem and ground transportation expenses. An honorarium is also given for each meeting.

6. Scheduling, Quorum, & Organization of Meetings

At the meetings of the NRN DSMC, it will review and make recommendations about the Study protocol(s) including frequency of interim analyses and whether data will or will not be masked to identify randomized groups.

The DCC provides logistics for meetings (both in person and teleconferences). It is expected that all DSMC members attend meetings. However, it is recognized that this may not always be possible. Therefore, the DSMC for the NRN has established the following quorum for voting. A quorum of this DSMC is considered to be 2/3rds of all voting members on the committee. If a member is absent the vote is considered abstain unless obtained in advance of the meeting. Quorum must be reached in order for an item to be voted on. At least 2/3's of the DSMC voting members must be present for meetings. At least one biostatistician member should be present or provide written comments in advance to the Chair and the DCC PI.

7. Materials and Protocol for DSMC Meetings

The agenda for DSMC meetings and calls will be drafted by the DCC in accordance with the study protocol. The DSMC Chair will review the finalized agenda prior to distribution to the group.

The agenda and meeting materials will be distributed to the DSMC by the DCC at least one week before each meeting or call, to allow members adequate time to prepare for the meeting. Meeting materials will include the following reports and data, as applicable:

- Interim data for monitoring as per the study protocol
- Adverse event data
- Other safety data
- Quality and completeness of study data
- Enrollment data
- Additional required reports / data as needed or requested
- Copy of study protocol and manual, as needed.

The DSMC will review the above information at each meeting to ensure proper conduct of the Study.

Meeting Protocol

DSMC meetings and calls for the *Neonatal Research Network* will be organized into open and closed sessions. Definitions for each of the meeting types are included below. The meeting type will be identified by the DCC when they provide the DSMC Chair with the meeting agenda.

- **Open sessions:** Information will be presented to the DSMC by the DCC, study investigators and NICHD staff as appropriate, with time for discussion.
- **Closed sessions:** The DSMC, DCC, and NICHD ES will discuss confidential data from the study, including information on efficacy and safety by treatment arm. The DSMC will remain masked to the treatment assignments at each meeting. The DSMC may request unmasking of the treatment assignment based on safety, efficacy, futility, or other compelling reason. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session. At the conclusion of the closed session, participants will re-convene so that the DSMC Chair can provide a summary of the DSMC's recommendations. This provides an opportunity for the NICHD Program Scientist and investigator(s) as needed,

the DCC, and NICHD to ask questions to clarify the recommendations. The meeting is then adjourned.

Proper records will be collected from each of the DSMC meetings to ensure there is a physical record of recommendations. The documentation that will be gathered from DSMC meetings for the *Neonatal Research Network* includes the following:

- Initial summary: The DCC is responsible for assuring the accuracy and transmission of a brief summary of the DSMC's discussion and recommendations to the Director, as necessary, and NICHD, in a timely manner. The Director or designee will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the clinical investigators.
- Formal minutes: The DCC is responsible for insuring availability of the formal DSMC minutes for the Director, as necessary, and NICHD, in a timely manner. These minutes are prepared to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting.
- Action plan: If the DSMC's recommendations require input from the Director of NICHD, significant changes or follow-up, NICHD staff and the DCC will collaborate to prepare an action plan outlining the steps required to implement the recommendations.

Minutes will be reviewed by the DCC, DSMC Chair and members for final review and approval. The DSMC Chair may sign the minutes or indicate approval electronically via email.

9. Reports of DSMC Proceedings for IRBs

The DCC is required to submit reports to IRBs at each of the participating sites following DSMC meetings.

If the DSMC does not identify any safety or other protocol-related concerns, after a DSMC meeting, the DCC will prepare a Summary Report that will state that the DSMC recommended that the study continue without modification of the protocol or informed consent.

If concerns are identified, the report to the clinical centers will outline the concerns, the DSMC discussion of the concerns, and, if necessary, the recommendations of the Director of NICHD.

The report will be distributed by the DCC to each clinical center involved in this Study. It is the responsibility of each clinical center PI to forward this information to the local IRB.

10. DSMC listing in NRN publications

The DSMC will be acknowledged as an independent panel in NRN publications. Names and affiliations of each DSMC member will be listed in the appendix of manuscripts.

Acceptance of DSMC Terms and Conditions Form

I, _____, member of the Data Safety and Monitoring Board for the *Neonatal Research Network*, agree to the terms outlined in this charter. If the charter is changed at any time, all DSMC members will review the changes and must agree to the new charter.

_____ _____ _____

Signature Printed Name Date

_____ _____ _____

DSMC Chair Signature Printed Name Date

Detach and submit form to NICHD Executive Secretary for the study.

Conflict of Interest Statement

I, _____, assuming the role of a DSMC member for the *Neonatal Research Network* agree to the following statements.

☐ I agree to:

- protect the interests and safety of study participants;
- uphold the integrity of the research process including data collection and analysis to be as free from bias and preconception as I am able;
- adhere to the highest scientific and ethical standards, to comply with all relevant regulations and to eliminate or disclose, during my involvement with the proposed clinical research project, any real or apparent conflicts of interest.

In addition:

☐ I declare that I, nor my spouse or dependent children, or organization with which I am connected, do/does not have any financial interest in the studies of the *Neonatal Research Network*, where financial interested is defined by the DHHS, as anything of monetary value, including but not limited to, salary or other payments for services (for example, consulting fees or honoraria); equity interests (for example, stocks, stock options or other ownership interests); and intellectual property rights (for example, patents, copyrights and royalties from such rights).

The financial interest term does not include various items which can be found in The Federal regulation, PHS, DHHS Part 50--Policies of General Applicability; Subpart F- *Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought.*

For Federal employees, financial interests that are allowable and require disclosure are:

Financial Interest Disclosure: Financial interest that require disclosure are stock holdings in pharmaceutical firms, medical device manufacturers, and biotechnology companies
Allowable Financial Interests: In a company that produces a product that is being evaluated by a study, participants may hold up to $15,000 of stock: and , up to an aggregate of $25,000 of the stock of that company and its competitors who produce that (or a similar) product. As an alternative to individual stock holdings, participants may hold up to an aggregate of $50,000 in sector mutual funds-including pharmaceutical/health care sectors.

For holdings in excess of these *de minimus* levels, a conflict of interest analysis needs to be conducted by NIH regarding the holding, the company producing the product being evaluated under the study, and its competitors, and, if a conflict exists, could lead to the need to withdraw from the study.

☐ I acknowledge that I have no known scientific conflicts of interest with the study.

☐ I will not engage in activities that could be viewed as real or apparent COI, including but not limited to:

- ☐ having a part-time, full-time, paid, or unpaid employee status of any organizations that are: (a) involved in the study under review; (b) whose products will be used or tested in the study under review, or whose products or services would be directly and predictably affected in a major way by the outcome of the study;
- ☐ being an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations;
- ☐ being a current collaborator or associate of the principal investigator (applicable to potential members of data safety and monitoring boards);
- ☐ having a scientific interest beyond that required for my role, where scientific interest is defined as having influence over the protocol, the study design, conducting the study analysis or any reporting related to the investigation (applicable to potential members of data safety and monitoring boards).

Signature	Printed Name	Date

DSMC Confidentiality Agreement

I understand that I will be provided with information from the Data Coordinating Center or Study sites or similar organizations for the *Neonatal Research Network* including proprietary and confidential information.

I understand that I will have access to these records in order to participate in the Data and Safety Monitoring Committee for the *Neonatal Research Network.*

In my role as a DSMC member, I _____, hereby agree that I shall not release, publish, or reproduce these records. I further agree that I shall not make any use of these records except for the limited purpose of participation in the Data and Safety Monitoring Committee for the *Neonatal Research Network.*

I will take reasonable precautions to prevent access by any other persons to these confidential records or to work products that result from review of those records. I will retain any confidential documentation until the conclusion of the Study and will return the documents and all related materials to the DCC for this Study.

I have read the terms of this agreement and agree to abide by its terms.

Signed: _____ Date: _____
[Name], [Title]

Appendix 1

NICHD Neonatal Research Network DSMC Membership Roster

6/25/2010

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NICHD Neonatal Research Network Additional DSMC Members for the SUPPORT Trial

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NICHD Neonatal Research Network Additional DSMC Members for the INOSITOL Trial

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Appendix

C

Advisory Board Members

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Neonatologist, Department of Pediatrics
Johns Hopkins Medical Institutions

Lawrence C. Gilstrap, MD
Chair Emeritus, Department of Obstetrics & Gynecology and Reproductive Sciences, University of Texas at Houston;
Clinical Professor, Obstetrics & Gynecology, University of Texas Southwestern;
Executive Director, American Board of Obstetrics & Gynecology

Alan H. Jobe, MD PhD
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Mark A. Klebanoff, MD MPH
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Richard Polin, MD
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Jun Jim Zhang, MD PhD
Epidemiology, Statistics, & Prevention Research, NICHD

Appendix

D

Illustrative Site Visit Agenda

DAY ONE

8:00 - 9:00 AM	Introduction of Network Staff/Organization/Overview 1. Introduction of new protocols to the department 2. In-services, training, etc 3. Typical day (schedule) 4. Weekend / Night coverage 5. Plans for current protocol recruitment 6. Regulatory compliance
9:00 - 9:30 AM	Tour of NICU and Level II Nursery 1. Identification of subjects
9:30 - 11:30 AM	Tour of data entry area and Network offices 1. Study manuals/protocols 2. Filing 3. Data entry procedures 4. Data verification/edit procedures 5. Study procedures/documentation 6. Responsibility for distribution of information
12:30 - 1:00 PM	Introduction to Follow-up staff/ Organization/Overview
1:00 - 2:00 PM	Tour Follow-up area - Charts/Forms
2:00 - 5:00 PM	Tracking and other Follow-up Issues 1. Identification of subjects; interaction with NICU teams 2. Discharge summary 3. Chart preparation 4. Schedule of 1st visit 5. Incentives (reimbursement) 6. Home visit 7. Ideas to improve compliance/share resources

DAY TWO

8:00 – 9:00 AM	Research pharmacy tour/organization of Network studies
9:00 – 10:00 AM	Respiratory therapists/organization/participation in ongoing Network studies
10:00 – 12:00 PM	Tour and overview of second site (if applicable)
1:00 – 2:00 PM	Feedback

Appendix

E

Sample Checklist for Adding Satellite Sites

Neonatal Research Network
Satellite Site Addition
Approval Process & Implementation

Date requested: _____
Name of Center: _____
PI: _____
Proposed Satellite: _____
Date all requirements completed: _____

Clinical centers wishing to add a satellite hospital must meet following requirements:		
Requirement	**Completion date**	**Initials**
Approval by **NICHD Program Officer**		
I. **Written Agreements**		
Formal written request submitted to the NICHD Program Officer and DCC PI and signed by the Center's PI and Business Official		
Copy of contractual agreement with proposed satellite hospital		
Agreement regarding co-authorship		
II. **Implementation Plan** – The plan must be submitted to the NICHD Program Officer and the DCC and should include copies and descriptions of the following:		
1. General information		
Name/contact information of IRB Chair		
% capitation to be paid to the satellite hospital		
% base budget (if applicable)		
(2) letters of support from proposed satellite hospital		

Clinical centers wishing to add a satellite hospital must meet following requirements:		
Requirement	**Completion date**	**Initials**
Co-authorship agreement		
2. Recruitment - A statement regarding the recruitment at the proposed satellite center should include the following:		
Total annual births <1,500 grams		
Expected GDB monthly recruitment		
3. Staffing – a description of the supervisory and staffing, including:		
CV of head investigator and head nurse at proposed satellite hospital; DCC primary contact		
NRN supervisory plans		
Proposed satellite center staff (i.e., study nurses, follow-up coordinator, research pharmacist, etc.)		
Proposed staff training, in-service, certification plans		
4. Data Management - Data collected at ancillary hospitals will be entered by the funded clinical center. Therefore, coordination between sites needs to be detailed and should include the following:		
Plans for data handling (collection, entry, transmission)		
Plans for quality assurance (timing and handling of edits and audits)		
Approval by **NICHD Grants Management Official**		
Federal Wide Assurance (FWA)		
IRB approval for each protocol to be conducted at proposed satellite hospital		
Approval by the **DCC**		
Training – The coordinator of the satellite center may be required to attend trainings at the discretion of the DCC and NICHD.		
Certification – Determination and priority of studies conducted at the site will be decided upon the DCC and NICHD		
Documentation of IRB approval must be received by the DCC and NICHD		
Consent forms - must be received and approved by the DCC and NICHD		

Clinical centers wishing to add a satellite hospital must meet following requirements:		
Requirement	**Completion date**	**Initials**
Equipment – must have (or have access to) the equipment necessary to conduct the proposed Network protocols, such as 20º freezer, centrifuge, etc.		
Pharmaceutical arrangements must be approved		
Study materials (protocol, manual of operations, forms, etc.) must be distributed for each protocol		
Letters of agreement from specific personnel responsible for specific procedures (e.g. audiologist, pediatric examiner)		

Other Requirements - additional documentation may be requested by the NICHD Program Officer, NICHD Grants Management Specialist, and/or the DCC Principal Investigator.

Appendix

F

Protocol Review Checklist

Protocol: _____

Study PI: _____

Center: _____

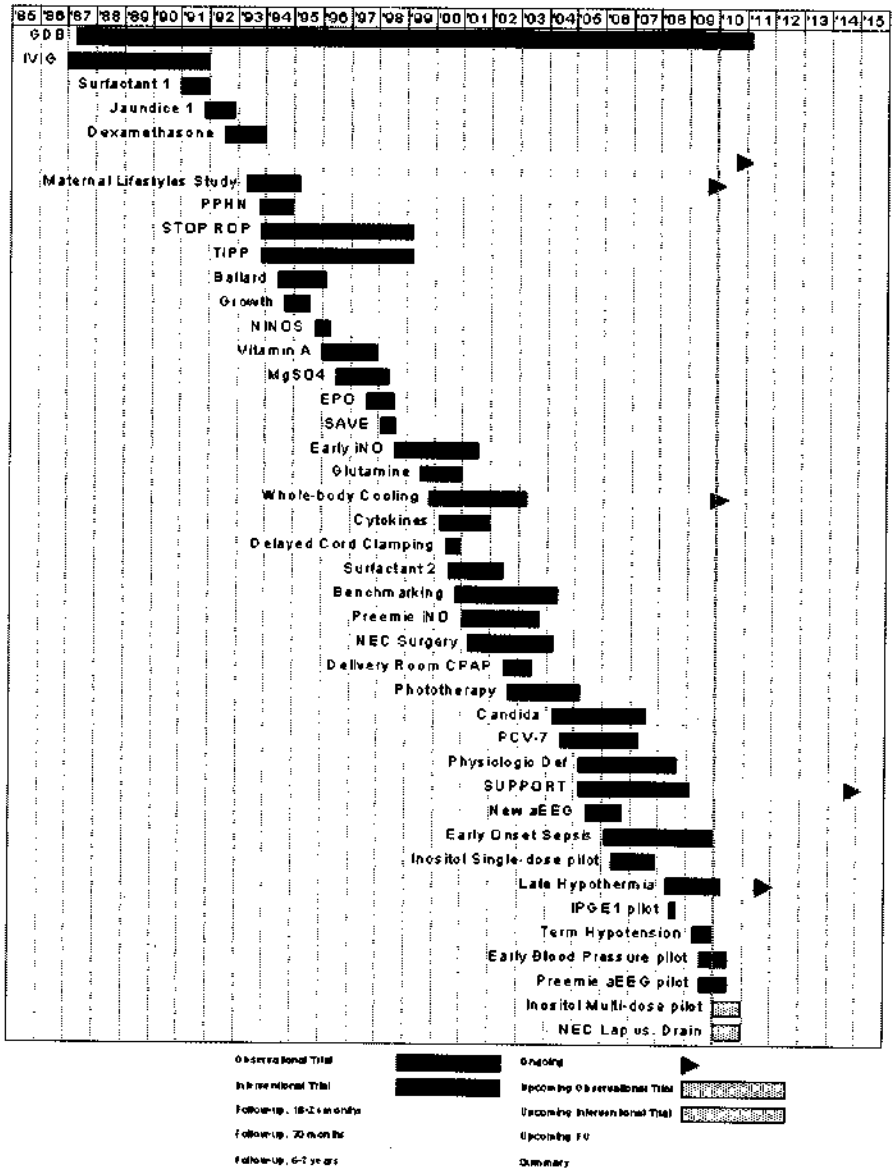
Date: _____

- ☐ Abstract/synopsis
- ☐ Statement of Problem
- ☐ Hypothesis
- ☐ Specific Aims
- ☐ Rationale/justification
- ☐ Background/Previous studies
- ☐ Methods/procedures
  - ☐ Description of study design (masked, randomized, etc.)
  - ☐ Definition of study population
  - ☐ Description of study intervention
  - ☐ Precise definition of primary/secondary outcomes
  - ☐ Sample size estimate with some statistical support (including estimate of compliance and consent rates) based upon primary outcome
  - ☐ Available population/compatibility with other ongoing protocols
  - ☐ Estimate of projected recruitment time
  - ☐ Anticipated Budget

Appendix

G

Network Trials Timeline (1987-2010)



Appendix

H

Specimen Transfer Agreement

A Specimen Transfer Agreement should include the final approved protocol (as an attachment), the date of the Steering Committee approval, and the following provisions:

1. RECIPIENT agrees to use the Material only for the approved Protocol. The RECIPIENT agrees that it will NOT use the Material for pilot or exploratory studies beyond that explicitly stated in the Protocol without written permission from the NICHD NRN Steering Committee. Any further study not described in the attached Protocol must be approved in writing by NICHD prior to being implemented.

2. RECIPIENT agrees to use the Material for non-profit research purposes only and will not use the Material for any commercial purposes, including selling, commercial screening, or transferring Material or any derivative thereof to a third party for commercial purposes.

3. THE RECIPIENT AGREES THAT THIS MATERIAL MAY NOT BE USED FOR ANY DIAGNOSTIC, PROGNOSTIC, OR TREATMENT PURPOSES.

4. PROVIDER will provide the RECIPIENT with DE-IDENTIFIED samples. The RECIPIENT will NOT contact or make any effort to identify individuals who are or may be the sources of the Material. Should any identifiable information be inadvertently transferred, the RECIPIENT's use of the Material is subject to:

    a. The Privacy Act of 1974, as amended, at 5 U.S.C. §552a ("Privacy Act") requirements; and
    b. Applicable human subjects regulations and guidance, which may include 45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56, and FDA Good Clinical Practice Guidelines (ICH E6 Good Clinical Practice: Consolidated Guidance, 62 FR 25692 (1997)).

5. The RECIPIENT will comply with all laws, rules, and regulations applicable to the handling and use of the Material, including following appropriate biological specimen security and handling protections. The RECIPIENT represents that it has obtained any required Institutional Review Board approval, as appropriate, to use the Material.

6. The RECIPIENT agrees to assume all liabilities related to the transferred biological specimens and their uses.

7. RECIPIENT will allow the use of the Materials only by the RECIPIENT's Investigator and the RECIPIENT Investigator's research team that are under the direct supervision of RECIPIENT Investigator and only after they have been informed of and agreed to the provisions and restrictions stated herein. Any transfer of Material to other than the RECIPIENT's Investigator's research team requires the advanced written approval of the NICHD Neonatal Research Network Steering Committee.

8. The RECIPIENT will abide by the NRN Policies and Procedures for Publications. The RECIPIENT will acknowledge the NICHD Neonatal Research Network's contribution of the Material in all relevant applications, presentations, and publications.

9. All Confidential Information that is transferred between PROVIDER and RECIPIENT is subject to the following:

   All information to be deemed confidential under the Agreement shall be clearly marked "CONFIDENTIAL" by the PROVIDER and maintained in confidence by the RECIPIENT.

10. When the Protocol is completed or the Agreement is terminated, whichever comes first, any unused Material will either be destroyed in compliance with all applicable statutes and regulations, or will be returned to the PROVIDER as requested by the NICHD NRN Steering Committee.

Copies of the fully executed agreement should be sent to the:
NRN Data Coordinator Center
NICHD Program Scientist

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Cunningham, Meg"
Subject: RE: SC Call
Date: Friday, June 14, 2013 3:41:00 PM

Yes – skipping coordinator call.

SC agenda:

SUPPORT Update
PAS deadlines
Upcoming SC meeting
New Business

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Cunningham, Meg [mailto:mcunningham@rti.org]
Sent: Friday, June 14, 2013 3:40 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SC Call

Hi Rose,

You are skipping next week's coordinators call, right? The following Tuesday we will have an SC call. Do you have an agenda prepared?

I will be out of the office (b)(6) and a couple of site visits. Copy Kris on everything!
Meg

Meg Cunningham, CCRP
RTI International
701 13th St. NW, Ste. 750
Washington, DC 20005
tel: 202-974-7837
fax: 202-728-2095

www.rti.org

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: *****Steering committee call - urgent June 11 3 PM***
Date: Wednesday, June 12, 2013 12:30:42 PM

http://www.nytimes.com/2013/06/06/health/watchdog-halts-action-on-researchers.html

Rose:

Just in case you did not read it.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 10, 2013 10:03 AM
To: richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org)
Subject: *****Steering committee call - urgent June 11 3 PM***
Importance: High

Hi
We will have an urgent steering committee call tomorrow at 3 PM to discuss a SUPPORT request that RTI, Dr. Carlo and Dr. Finer have received. Abhik will send the request.

Call in information:

Tues. June 11 at 3 PM ET

(b)(6) with pass code
(b)(6)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E] (spongc@dir49.nichd.nih.gov); Maddox, Yvonne (NIH/NICHD) [E]
Subject: FW: (b)(5)
(b)(5)
Date: Wednesday, June 12, 2013 11:56:00 AM
Attachments: RTI DCC application.pdf
NRN Poloicies and procedures.pdf

FYI
Will keep you updated
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: McGarey, Barbara (NIH/OD) [E]
Sent: Wednesday, June 12, 2013 11:38 AM
To: Bonham, Valerie (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: (b)(5)
(b)(5)

(b)(5)

Thanks,

Barb

Barbara M. McGarey, J.D.
Deputy Associate General Counsel for Public Health, NIH
Office of the General Counsel, PHD, NIH Branch
31 Center Drive, Rm 2B-50
Bethesda, MD 20892-2111
(301) 496-6043 (phone)
(301) 402-1034 (fax)
mcgareyb@od.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, June 11, 2013 5:13 PM
To: McGarey, Barbara (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: FW: (b)(5)

(b)(5)

(b)(5) Let me know what you think.

Thanks for your help.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:03 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: (b)(5)

(b)(5)

Hi

(b)(5)

Let me know if there are questions.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 7:41 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: (b)(5)
(b)(5)

More on the most recent info request, which did not come to us, of course (we were only cc:ed), but only to the investigators and RTI...

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, June 09, 2013 10:16 PM
To: Muroff, Julie (NIH/OD) [E]
Cc: McGarey, Barbara (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]
Subject: Re: (b)(5)
(b)(5)

Thank you so much Julie. It is (b)(5)
(b)(5) I guess that is why our jobs are quietly entertaining.

I am sharing via cc your opinion with pat white and Alan Guttmacher. (For reasons I do not understand my iPhone thinks Alan should be with caps but not pat.).

Alan - we look forward to response from nichd. pat, we look forward to an explanation of why your name is not capitalized.

Warmly,
Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy

NIH
301 496 1455
kathy.hudson@nih.gov

On Jun 9, 2013, at 7:51 PM, "Muroff, Julie (NIH/OD) [E]" <muroffj@od.nih.gov> wrote:

(b)(5)

We would be happy to elaborate by phone or meeting.

Julie A. Muroff, J.D., LL.M.
Senior Attorney
HHS Office of the General Counsel, PHD, NIH Branch
31 Center Drive, Bldg. 31, Rm.2B-47
Bethesda, MD 20892
301-451-4910 (direct)
301-402-1034 (Fax)
Julie_Muroff@nih.gov

From: McGarey, Barbara (NIH/OD) [E]
Sent: Friday, June 07, 2013 10:47 PM
To: Rockey, Sally (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: Re: (b)(5)

(b)(5)

We will take a look and advise.

From: Rockey, Sally (NIH/OD) [E]
Sent: Friday, June 07, 2013 09:58 PM
To: Hudson, Kathy (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: (b)(5)

(b)(5)

(b)(5)

(b)(5)

Sally J. Rockey, Ph.D.
NIH Deputy Director for Extramural Research
OD/NIH/DHHS
One Center Drive
Building 1, Room 144
Bethesda, MD 20892
301-496-1096 (BLDG. 1)
301-435-2698 (ROCK I)
301-402-3469 Fax
rockeysa@od.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, June 07, 2013 9:29 PM
To: Rockey, Sally (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: (b)(5)
(b)(5)

(b)(5)

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, June 07, 2013 5:19 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

FYI...

Alan

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: adas@rti.org; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

From: Finer, Neil
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Correspondence re: Your New England Journal of Medicine Article
Date: Wednesday, June 12, 2013 6:50:47 AM

I believe that we should either make no comment and not recommend publication if we have a choice, or we could state that we believe more involvement with parents in all phases of future study design and implementation
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 5:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: FW: Correspondence re: Your New England Journal of Medicine Article

Hi Rose and Neil:

This just came in. I think we should respond because NEJM is asking us to but we need to think of what we should say as it is not directly related to SUPPORT.

Should we bring this up during the call? Indeed, the NRN could develop a parent group.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

-----Original Message-----
From: onbehalfof+letter+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+letter+nejm.org@manuscriptcentral.com] On Behalf Of letter@nejm.org
Sent: Tuesday, June 11, 2013 10:09 AM
To: Wally Carlo, M.D.
Subject: Correspondence re: Your New England Journal of Medicine Article

Dear Dr. Carlo:

The attached correspondence regarding your recent article is under consideration for possible publication in a forthcoming issue. We would like to give you the opportunity to reply to the two (2) letters in print, with the stipulations that your reply not exceed 350 words of text and five references, and that we receive your letter within two weeks. Replies are subject to editing.

Your reply is due at the Journal by June 25. Notify the editorial office immediately via email to letter@nejm.org if you do not intend to respond.

Please understand that we will not make decisions regarding possible acceptance of the letters until after we receive

your reply.

No more than three persons may be listed as authors of your reply.

You should inform us in your covering letter if you or any co-authors have any financial relationships with any company whose products are mentioned in the letter or a company making a competing product. Please include any new relationships that may have developed since the publication of your manuscript.

Should your letter be accepted, there should be no announcements or news releases about your letter until the day before the date of publication.

If there are any questions about these policies, you should call to discuss them.

To submit your reply, please visit http://authors.nejm.org and log in. Your case-sensitive USER ID is wcarlo@peds.uab.edu. For security purposes your password is not listed in this email. If you are unsure of your password you may click the link below to set a new password.

http://mc05.manuscriptcentral.com/nejm?URL_MASK=RqjwPqfMtrtMBNMTnhSs

Once you are logged in, the Main Menu will be displayed. Please click on the Author Center, where you will find the reply letter listed under "Invited Manuscripts." You can click on the "Continue Submission" button to begin submitting your reply letter.

Thank you for your interest in the Journal.

Sincerely,

Joe Piccirillo
Manager of Editorial Systems Workflow
New England Journal of Medicine
617.487.6587: Direct
617.739.9864: Fax

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
http://www.nejm.org

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Seetha Shankaran "
Subject: FW: *****Steering committee call - urgent June 11 3 PM***
Date: Tuesday, June 11, 2013 3:51:00 PM
Attachments: SUPPORT Letters to the Editor.pdf

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 3:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org)
Subject: RE: *****Steering committee call - urgent June 11 3 PM***

Enclosed are two letters from NEJM.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R

Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 10, 2013 10:03 AM
To: richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org)
Subject: *****Steering committee call - urgent June 11 3 PM***
Importance: High

Hi
We will have an urgent steering committee call tomorrow at 3 PM to discuss a SUPPORT request that RTI, Dr. Carlo and Dr. Finer have received. Abhik will send the request.

Call in information:

Tues. June 11 at 3 PM ET

(b)(6) with pass code

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Date Submitted: 24-May-2013
Ms. Number: 13-06780

Corr-Au: Dr. William Tarnow-Mordi
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Hawkesbury Road
Sydney, New South Wales 2145
Australia
E-Mail: williamtm@med.usyd.edu.au
Publish? Yes

Articles Referenced: May 16, 2013: Risk, Consent, and SUPPORT

To the Editor:

Magnus and Caplan(1) rightly conclude that criticisms of consent processes by the Office of Human Research Protections pose substantial risk to comparative effectiveness research, in all specialties. Looking forward, recommendations by US,(2, 3) UK(3) and Australian government agencies, some as recent as 2010, (2) provide a strategy to address this risk, by engaging consumers as partners throughout the research process. This includes engagement in prioritizing and designing studies, trial conduct, preparing study information, recruitment and interpreting and disseminating results. Outside the UK,(4) few trials in any field have yet realized this goal. Achieving it requires appropriate resources to train and support consumers as effective research partners.

Consumers can also be effective advocates. After her newborn daughter died at home from undiagnosed heart disease, one of us successfully lobbied Indiana to mandate pulse oximetry screening for congenital heart disease in all newborns. (5) This is now US federal policy. Consumer advocates could help broaden public support and participation in clinical research, to avert the threat of a significant slowdown in improvements in clinical care and survival.(1)

William Tarnow-Mordi,
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Melinda Cruz,
B.Sc.

Miracle Babies Foundation (Registered Charity),
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Chipping Norton, NSW 2170, Australia

Kristine Brite McCormick

Cora's Story, Inc. (Not for profit)
Indianapolis, Indiana, ~~United States~~

~~Tarnow-Mordi, William; Brite McCormick, Kristine; Cruz, Melinda~~
~~University of Sydney, , Cora's Story, Miracle Babies Foundation~~

~~**Disclosure:** None~~No potential conflict of interest relevant to this letter was reported.

1. Magnus D, Caplan AL. Risk, consent, and SUPPORT. N Engl J Med. 2013 May16; 368(20):1864-5
2. Washington AE, Lipstein SH. The Patient-Centered Outcomes Research Institute--promoting better information, decisions, and health. N Engl J Med. 2011 Oct 13;365(15):e31.
3. Tarnow-Mordi WO, Cruz M, Wilkinson D. Evaluating therapeutic hypothermia: parental perspectives should be explicitly represented in future research. Arch Pediatr Adolesc Med. 2012 Jun 1;166(6):578-9.
4. Stewart D, Wilson R, Selby P, Darbyshire J. Patient and public involvement. Ann Oncol. 2011 Nov;22 Suppl 7:vii54-vii56.
5. McCormick KB. Pulse oximetry advocacy. http://pulseoxadvocacy.com/ accessed 19 May 2013.

Date Submitted: 24-Apr-2013
Ms. Number: 13-05412

Corr Au: Prof. Leonard Glantz
Boston University
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Talbot Building
Boston, Massachusetts 02118
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E-Mail: lglantz@bu.edu
Publish? Yes

Articles Referenced: Online Articles: Risk, Consent and the SUPPORT Study

To the Editor:

The central defense of the ethics of the SUPPORT trial is that the subjects were not put at increased risk of harm because they were randomized into two groups which both provided the â€œstandard of care.â€ —If the babies could not be harmed by randomization it would be equally true that they could not benefit. However, the consent formâ€™s benefit section states â€œIt is possible that that using lowered pulse oximeter ranges will result in fewer babies with severe retinopathy (ROP)â€ — There is no equivalent language that babies in the higher oxygenation arm might â€œpossiblyâ€ suffer more retinopathy. Nor is there any language that suggests the â€œpossibilityâ€ that lower levels of oxygenation could lead to an increase in deaths. This is especially troubling given the investigatorâ€™s statement that â€œDeath was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.â€ —The fact that â€œdeath competes with retinopathyâ€ underscores the need for language in the consent form to counterbalance the optimistic language in the benefits section.

Leonard H. Glantz, J.D.
Michael A. Grodin, M.D.

Both at
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Glantz, Leonard H.; Grodin, Michael
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Disclosure: NoneNo potential conflict of interest relevant to this letter was reported.

1. Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely preterm infants. N Engl J Med 2013. DOI: 10.1056/ NEJMc130482

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Correspondence re: Your New England Journal of Medicine Article
Date: Tuesday, June 11, 2013 2:52:00 PM

Sure
Rose

Rosemary D. Higgins, MD
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-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 2:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Correspondence re: Your New England Journal of Medicine Article

Should I sent the letters to all on the call today?

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 11, 2013 1:49 PM
To: Wally Carlo, M.D.
Subject: RE: Correspondence re: Your New England Journal of Medicine Article

Just read it - deserves a response!

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 2:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Correspondence re: Your New England Journal of Medicine Article

Rose

Notice the second letter.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 11, 2013 10:18 AM
To: Wally Carlo, M.D.; Finer, Neil
Subject: RE: Correspondence re: Your New England Journal of Medicine Article

Sure- bring it up on the call.

Rose

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Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
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-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 11:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: FW: Correspondence re: Your New England Journal of Medicine Article

Hi Rose and Neil:

This just came in. I think we should respond because NEJM is asking us to but we need to think of what we should say as it is not directly related to SUPPORT.

Should we bring this up during the call? Indeed, the NRN could develop a parent group.

Wally

Wally Carlo, M.D.
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-----Original Message-----
From: onbehalfof+letter+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+letter+nejm.org@manuscriptcentral.com] On Behalf Of letter@nejm.org
Sent: Tuesday, June 11, 2013 10:09 AM
To: Wally Carlo, M.D.
Subject: Correspondence re: Your New England Journal of Medicine Article

Dear Dr. Carlo:

The attached correspondence regarding your recent article is under consideration for possible publication in a forthcoming issue. We would like to give you the opportunity to reply to the two (2) letters in print, with the stipulations that your reply not exceed 350 words of text and five references, and that we receive your letter within two weeks. Replies are subject to editing.

Your reply is due at the Journal by June 25. Notify the editorial office immediately via email to letter@nejm.org if you do not intend to respond.

Please understand that we will not make decisions regarding possible acceptance of the letters until after we receive your reply.

No more than three persons may be listed as authors of your reply.

You should inform us in your covering letter if you or any co-authors have any financial relationships with any company whose products are mentioned in the letter or a company making a competing product. Please include any new relationships that may have developed since the publication of your manuscript.

Should your letter be accepted, there should be no announcements or news releases about your letter until the day before the date of publication.

If there are any questions about these policies, you should call to discuss them.

To submit your reply, please visit http://authors.nejm.org and log in. Your case-sensitive USER ID is wcarlo@peds.uab.edu. For security purposes your password is not listed in this email. If you are unsure of your password you may click the link below to set a new password.

http://mc05.manuscriptcentral.com/nejm?URL_MASK=RqjwPqfMtrtMBNMTnhSs

Once you are logged in, the Main Menu will be displayed. Please click on the Author Center, where you will find the reply letter listed under "Invited Manuscripts." You can click on the "Continue Submission" button to begin submitting your reply letter.

Thank you for your interest in the Journal.

Sincerely,

Joe Piccirillo
Manager of Editorial Systems Workflow
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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Correspondence re: Your New England Journal of Medicine Article
Date: Tuesday, June 11, 2013 2:49:44 PM

Agree. I will draft it.

Wally Carlo, M.D.
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Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics

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From: onbehalfof+letter+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+letter+nejm.org@manuscriptcentral.com] On Behalf Of letter@nejm.org
Sent: Tuesday, June 11, 2013 10:09 AM
To: Wally Carlo, M.D.
Subject: Correspondence re: Your New England Journal of Medicine Article

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Joe Piccirillo
Manager of Editorial Systems Workflow
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From: Gantz, Marie
To: WCarlo@peds.uab.edu; nfiner@ucsd.edu; wrich@ucsd.edu; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; Michele.Walsh@UHhospitals.org; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT ROP/SpO2 secondary paper
Date: Thursday, July 11, 2013 2:25:54 PM
Attachments: ROP secondary 2013-07-11 with notes.docx

Hi all,

Attached is a long-overdue draft of the ROP/SpO2 secondary paper for SUPPORT. The target journal is J Perinatology. I would appreciate it if you would review and send comments/edits by July 26. Thanks in advance.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

Oxygen Saturations and Retinopathy of Prematurity in Extremely Preterm Infants

Marie G. Gantz, Ph.D.[1]; Waldemar A. Carlo, M.D.[2]; Neil N. Finer, M.D.[3]; Wade Rich, RRT[3]; Roger G. Faix, M.D.[4]; Bradley Yoder, M.D.[4]; Michele C. Walsh, M.D., M.S.[5]; Nancy Newman, R.N.[5]; Abbot Laptook, M.D.[6]; Kurt Schibler, M.D.[7]; Abhik Das, Ph.D.[8]; Rosemary D. Higgins, M.D.[9]; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

[1]RTI International, Research Triangle Park, North Carolina; [2]University of Alabama at Birmingham, Birmingham, Alabama; [3]University of California, San Diego, San Diego, California; [4]University of Utah, Salt Lake City, Utah; [5]Case Western Reserve University, Cleveland, Ohio; [6]Women and Infants Hospital of Rhode Island, Providence, Rhode Island; [7]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [8]RTI, Rockville, Maryland; [9]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Corresponding author and reprints:

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Short title: Oxygen saturations and retinopathy of prematurity

Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute

Word count

Abstract: 145

Text: 2,786

Abbreviations:

AOR = Adjusted odds ratio

CI = Confidence interval

GA = Gestational age

IVH = Intraventricular hemorrhage

NEC = Necrotizing enterocolitis

PMA = Postmenstrual age

PVL = Periventricular leukomalacia

ROP = Retinopathy of prematurity

SGA = Small for gestational age

SpO_2 = Oxygen saturation

ABSTRACT

Objective

To identify specific oxygen saturation levels associated with severe ROP among infants in the SUPPORT trial.

Study Design

Data on oxygen saturation and supplementation were collected up to 36 weeks postmenstrual age or severe ROP determination for 984 surviving infants. Logistic regression models were created to predict severe ROP.

Result

Percentage of days on supplemental oxygen (adjusted odds ratio (AOR) for a 5% increase 1.14, 95% CI 1.06 – 1.22), center, lower gestational age, small for gestational age (<10th percentile), severe illness (fraction of inspired oxygen > 0.4 and on ventilator for > 8 consecutive hours in the first 14 days of life), and late onset sepsis or meningitis were predictors of severe ROP.

Conclusion

Among infants who survived to discharge, those with severe ROP spent significantly more time on oxygen supplementation.

Keywords

Infant Mortality, Newborn, Infant, Oximetry, Oxygen/administration & dosage, Oxygen Inhalation Therapy/adverse effects

Introduction

Retinopathy of prematurity (ROP) is an important cause of blindness and other visual disabilities in preterm infants. The occurrence of ROP is indirectly proportional to gestational age, but high oxygen exposure has been associated with increased risk of retinopathy. The incidence of ROP decreased with exposure to restricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.[1] However, the resultant practice of restricting oxygen supplementation, usually to no more than 50% inspired oxygen concentration was estimated to result in an excess of 16 deaths per case of blindness prevented.[2]

In the SUPPORT trial, 1316 infants born at gestational ages of 24 0/7 weeks to 27 6/7 weeks between February 2005 and February 2009 were randomized to oxygen saturation target ranges of either 85-89% or 91-95%. Severe ROP among survivors was decreased in the lower (85-89%) oxygen saturation target group compared to the higher (91-95%) oxygen saturation target group (relative risk 0.52, 95% confidence interval (CI) 0.37 – 0.73, $p < 0.001$, number needed to treat = 11), and the duration of oxygen supplementation among survivors was shorter.[3] However, mortality was increased in the lower oxygen saturation group. Two similarly designed trials have been terminated prematurely due to similar mortality findings.[5]

Data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of ROP relative to low normal levels.[6-8] In three pre-post design studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[7,11,12] Although a multicenter observational study did not report a significant association between partial pressure of oxygen (PaO_2) levels and retinopathy,[9] a single center cohort study using transcutaneous oxygen

Comment [MG1]: Wally: Correct?

monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels ≥ 80 mmHg.[10] While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ROP, concerns remain about the safety of low oxygen saturation targets and about the specific oxygen saturation levels that are associated with ROP.

Thus, there is a need to determine the oxygen saturation levels that were associated with severe ROP among survivors in the SUPPORT trial to assist in the selection of safe oxygen saturation targets that optimize survival but do not increase the risk of severe ROP. This is important because the actual oxygen saturation levels achieved differed from the targets in SUPPORT, and the oxygen saturations while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably. Furthermore, it is likely that the overall duration of oxygen supplementation and other demographic characteristics and neonatal morbidities are associated with a higher risk of severe ROP. This study tests the hypothesis that there are oxygen saturation levels that increase the risk of severe ROP independent of other baseline characteristics. It also tests the hypothesis that duration of oxygen exposure, demographic characteristics, gestational age, and neonatal morbidities will be associated with a higher risk of severe ROP independent of other characteristics.

Subjects and Methods

This was a secondary analysis of the data from the oxygen saturation SUPPORT trial. As described previously,[3] surviving infants were followed by ophthalmologists trained in the diagnosis of ROP. Examinations began by 33 weeks' postmenstrual age (PMA) and continued until the severe ROP outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group[13,14]) was diagnosed if any of the following findings were present: in zone 1, stage 3 ROP, even

without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; in zone 2, plus disease with stage 2 ROP or plus disease with stage 3 ROP. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. Severe retinopathy was defined as threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy.

Respiratory support data, including mode of support and fraction of inspired oxygen, were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life and once a day from 15 days of life through 36 weeks' PMA or death, transfer or discharge. After February 2006, respiratory support data were collected every two hours for the first 14 days of life and every 6 hours thereafter through 36 weeks' PMA or death, transfer or discharge.

Oxygen saturation data sampled every 10 seconds were collected while infants were receiving oxygen supplementation. Use of the study pulse oximeters was discontinued at 36 weeks' PMA or when the infant had been without respiratory support for three days, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks' PMA, the study oximeter was placed back on the infant.

Masking of treatment assignment was maintained using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, oxygen saturation (SpO_2) values in the correct target range were displayed as 88-92% (a maximum variation of 3% from the actual value). Display, not actual, SpO_2 values were recorded; thus, the data required transformation to actual saturation values prior to analysis. For some SpO_2 values there was not a one-to-one correspondence between display and actual values (specifically, for 84-85% and 93-96% in the low target group, 84-87% and 95-96% in the high target group). In these ranges, the number of seconds spent at each SpO_2

value was interpolated using a quadratic curve, ensuring that the total number of seconds was conserved. In cases where this method resulted in interpolation of a negative number of seconds, cubic Hermite interpolation, constrained to produce non-negative results, was used instead.

Oxygen saturations could only be targeted to assigned ranges while the infant was receiving supplemental oxygen. Furthermore, previous unpublished analyses of the SUPPORT pulse oximeter data revealed that infants spent more time with SpO_2 values of 97-100% on days when they did not receive supplemental oxygen compared to days on oxygen. For these reasons, this analysis included only those pulse oximeter data collected during oxygen supplementation. We considered the oximeter data to be for time on supplemental oxygen if the infant was receiving oxygen at the closest time point for which respiratory support data were collected on daily study forms. Pulse oximeter data from dates after the eye exam at which the ROP outcome (either severe ROP or resolution) was determined were excluded from this analysis.

The percent of time spent at various SpO_2 values while receiving supplemental oxygen was compared graphically for infants with and without severe ROP. The relationship between severe ROP and the amount of time spent on supplemental oxygen was explored using chi-square and Wilcoxon rank sums tests. Both the total number of days and the percentage of days spent on supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination were examined, and the Pearson correlation between the two measures was assessed.

Exploratory multivariate analysis was used to assess the relationship between severe ROP and the percent of time spent at each SpO_2 value (<70%, 70%, 71%, ..., 100%) while on oxygen supplementation. The result of this analysis was a linear combination of the percentages of time at each SpO_2 value that best discriminated between infants with and without severe ROP. This discriminant

function was interpreted by measuring the correlation between it and the original percentages of time at each SpO_2 value.

SpO_2 values found to be most highly associated with severe ROP in the multivariate analyses were included as covariates in logistic regression models predicting severe ROP. Because of previous associations found between ROP and higher oxygen saturations, the percentages of time spent in the SpO_2 ranges of 96-100%, 97-100%, 98-100%, 99-100%, and 100% were also explored as predictors of severe ROP. Additional covariates were the amount of time spent on supplemental oxygen (both the number of days and percent of days on oxygen were evaluated as potential predictors) and demographic and neonatal characteristics. Selection of demographic and neonatal characteristics was based on possible association with ROP and included clinical center, gender, race/ethnicity, gestational age (GA), small for gestational age ($<10^{th}$ percentile)[4] (SGA), any receipt of antenatal steroids, severe illness defined as $FiO_2 > 0.4$ and being on a ventilator for > 8 consecutive hours in the first 14 days of life, time weighted carbon dioxide (CO_2) in the first 14 days of life, periventricular leukomalacia (PVL), grade III or IV intraventricular hemorrhage (severe IVH), necrotizing enterocolitis (NEC), and late-onset sepsis or meningitis. For PVL, severe IVH, NEC, and late-onset sepsis or meningitis, only morbidities that occurred before the date of severe ROP outcome determination were included.

Separate analyses were conducted for all infants who survived to discharge and had a severe ROP outcome determined and for the subset of infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination. Due to the reduced number of infants available for the second analysis, the logistic regression model was reduced using backward selection, and only predictors that were statistically significant at the $p < 0.05$ level were retained in the final model.

Results

Of the 984 SUPPORT infants who survived to discharge and had the severe ROP outcome determined, 132 (13%) were diagnosed with severe ROP. The median number of days on which supplemental oxygen was received was 67 for infants with severe ROP (interquartile range (IQR) 54 – 74) and 43.5 for infants without severe ROP (IQR 18 – 63) (Wilcoxon rank sums test $p < 0.001$). Ninety-five percent (125/132) of infants with severe ROP received supplemental oxygen on at least half of the days prior to 36 weeks' PMA or severe ROP outcome determination compared to 64% (541/852) of infants without severe ROP (chi-square $p < 0.001$). Forty-five percent (60/132) of infants with severe ROP received supplemented oxygen every day compared to 17% (142/852) of infants without severe ROP (chi-square $p < 0.001$). The correlation between number of days and percent of days with supplemental oxygen was high (0.82 among those with severe ROP and 0.94 among those without severe ROP).

Ninety-five percent (932/984) of SUPPORT infants who survived to discharge and had a ROP outcome determined had oxygen saturation data available. Figure 1 compares the percent of time spent at each SpO_2 value while receiving supplemental oxygen for infants with and without severe ROP. The distributions were similar for the two groups, particularly with respect to the median percent of time spent at each SpO_2 value. In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with SpO_2 values less than 80% (correlations between the discriminant function and percentages of time at SpO_2 values < 80% were all > 0.5) (Figure 2). In logistic regression analysis adjusted for other risk factors, percent of days on supplemental oxygen prior to 36 weeks' PMA or severe ROP outcome determination was predictive of severe ROP (adjusted odds ratio (AOR) for a 5% increase in percent of days on supplemental oxygen: 1.14, 95% CI 1.06 – 1.22, $p < 0.001$), but percent of time while on supplemental oxygen with $SpO_2 < 80\%$ was not (AOR for a 5% increase in percent of time with $SpO_2 < 80\%$: 1.03, 95% CI 0.68 – 1.56, $p = 0.89$). Other significant

Comment [WC2]: Is there a statistical test that we should do to prove that they are similar?

MG: I am working on whether I can do a statistical test comparing these distributions.

predictors in the model were severe illness, late-onset sepsis or meningitis, GA, SGA, and clinical center (Table). When the percentages of time spent in SpO_2 ranges between 96% and 100% were investigated as predictors of severe ROP, none were statistically significant. When number of days was substituted for percent of days receiving supplemental oxygen, it did not reach significance as a predictor of severe ROP (AOR 1.02, 95% CI 0.999 – 1.03, p = 0.06); otherwise model results were similar.

Figure 3 compares the percent of time spent at each SpO_2 value while receiving supplemental oxygen for infants with and without severe ROP among the 202 infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination. The distributions were similar for infants with and without severe ROP, although infants with severe ROP spent a slightly higher percent of time with saturations near 100%. In multivariate analysis of this subset of infants, severe ROP was most highly associated with a greater percentage of time with an SpO_2 of 100% (correlation of 0.35 between discriminant function and percentage of time with SpO_2 = 100%) (Figure 2). This variable was also significant in the logistic regression model to predict severe ROP (AOR for a 5% increase in percent of time with an SpO_2 of 100%: 2.71, 95% CI 1.05 – 6.96, p = 0.04). Other significant predictors were severe illness, late-onset sepsis or meningitis, male gender, GA, and SGA (Table). When the percentage of time with an SpO_2 of 100% was replaced in the model by percentages of time spent in other SpO_2 ranges between 96% and 100%, the ranges of 99-100% and 96-100% were statistically significant (AOR for a 5% increase in percent of time with SpO_2 99-100%: 1.68, 95% CI 1.02 – 2.77, p = 0.04; AOR for a 5% increase in percent of time with SpO_2 96-100%: 1.27, 95% CI 1.04 – 1.55, p = 0.02) (Figure 4) while estimates for other predictors in the model remained similar. Number of days receiving supplemental oxygen was not a significant predictor of severe ROP in this subgroup of infants.

Comment [WC3]: Statistical test needed to prove similarity?

MG: I am working on whether I can do a statistical test comparing these distributions.

Comment [WC4]: Significant? Do we need "slightly"?

MG: I am working on whether I can do a statistical test comparing these distributions.

Comment [WC5]: How about other ranges (e.g. 97-100%, 96-99%, etc)? It is very important if these are NS.

MG: I want to avoid adding too many overlapping tests. What we have done so far is consistent with the analysis that was presented at PAS.

Discussion

Infants enrolled in SUPPORT who survived to discharge and were diagnosed with severe ROP spent significantly more time on supplemental oxygen on the days leading up to 36 weeks' PMA or severe ROP outcome determination compared to survivors without severe ROP. Logistic regression modeling showed that more time on oxygen was a significant risk factor for severe ROP after adjusting for baseline covariates. For infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination, a greater percentage of time with an oxygen saturation of 100% was a significant risk factor for severe ROP. The percentages of time spent in SpO_2 ranges of 99-100% and 96-100% were also statistically significant predictors, but the odds ratios decreased as the ranges expanded away from 100%. These results support the idea that the primary modifiable risk factors for severe ROP may be limited to avoiding extremely high oxygen saturations and reducing the amount of time spent on supplemental oxygen. Notably, surviving infants in the SUPPORT trial who were randomized to a lower oxygen saturation target (85-89%) spent fewer days on supplemental oxygen compared to those randomized to a higher oxygen saturation target (91-95%).[3]

[Need to add more interpretation of results.]

A limitation of the study is that some oximeter data needed to be interpolated due to the lack of a one-to-one match between the skewed SpO_2 values displayed by the oximeters and actual saturations. However, this did not affect SpO_2 values below 84% or above 96% which were of greatest interest in this analysis. Another limitation is that oximeter data for time on supplemental oxygen were identified based on the closest time point at which respiratory support data were captured on study forms. As respiratory support data were not continuously reported, it is possible that some oximeter data for times when the infants were not actually receiving supplemental oxygen were included in this analysis. Based on previous unpublished analyses of the SUPPORT oximeter data, the most likely impact of including

time not on oxygen support would be an increase in oximeter readings with oxygen saturations near 100%.

Other trials designed to target oxygen saturations similarly to SUPPORT have been completed[5] and could perform similar analyses. Previous large studies of associations of oxygen saturation levels and ROP reported targeted but not achieved saturations.[7-9]

In conclusion, a greater proportion of days with receipt of supplemental oxygen prior to 36 weeks' PMA is one of the strongest predictors of severe ROP. Severe pulmonary disease, late-onset sepsis or meningitis, PVL, SGA, lower GA, and center were other predictors of severe ROP. Among infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination, less time spent on oxygen with an SpO_2 of 100% was associated with a decrease in severe ROP. These results support the concept that infants with prolonged oxygen need are at high risk for severe ROP. This effect is larger than the effects of time spent in specific oxygen saturation ranges.

Comment [WC6]: I have to read more papers on the subject to put our results in perspective of the most pertinent literature.

Acknowledgements

These should be brief, and should include sources of support including sponsorship (e.g. university, charity, commercial organization) and sources of material (e.g. novel drugs) not available commercially.

Conflict of interest

Authors must declare whether or not there is any competing financial interests in relation to the work described. This information must be included at this stage and will be published as part of the paper. Conflict of interest should also be noted on the cover letter and as part of the submission process. See the Conflict of Interest documentation in the Editorial Policy section for detailed information.

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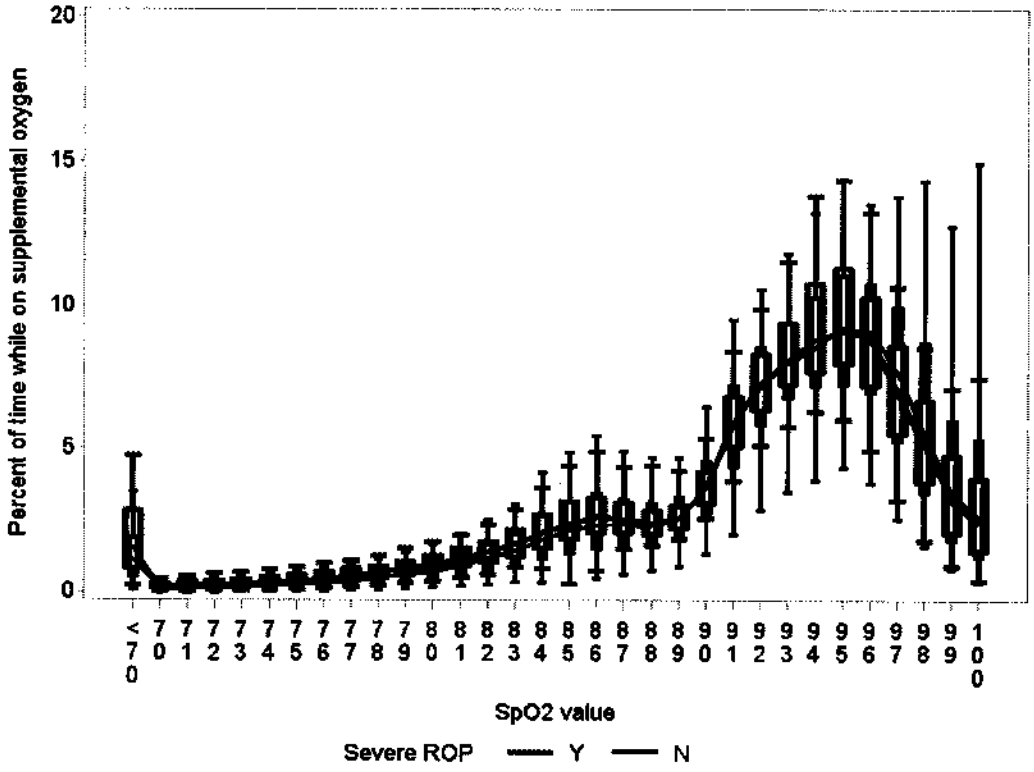
Figure 1. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination (N=932)

Comment [WC7]: I prefer to include interpretation of the results in figures legends also. Most journals use that style.



Boxes represent 25th to 75th percentiles. Whiskers represent 5th to 95th percentiles. Lines connecting the boxes represent medians.

Figure 2. Correlation between discriminant functions from multivariate analyses and percentage of time spent at each SpO2 value while on supplemental oxygen: a measure of association between percentage of time spent at each SpO2 value and severe ROP

Comment [MG8]: I would be alright with getting rid of this figure if it seems confusing.

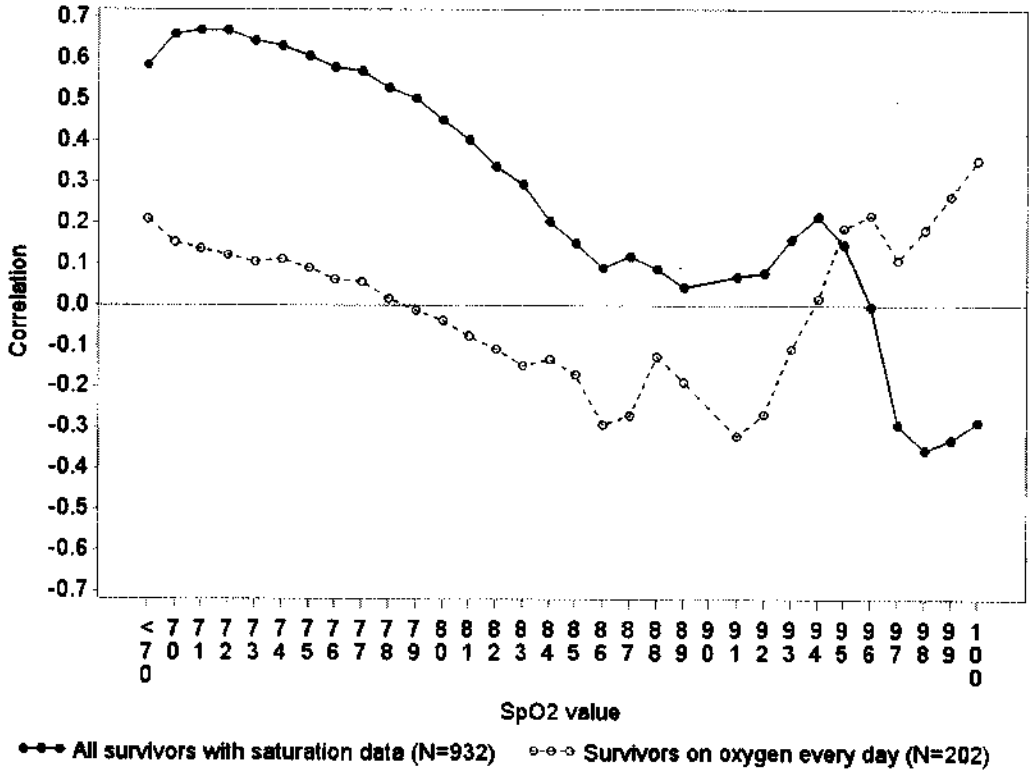
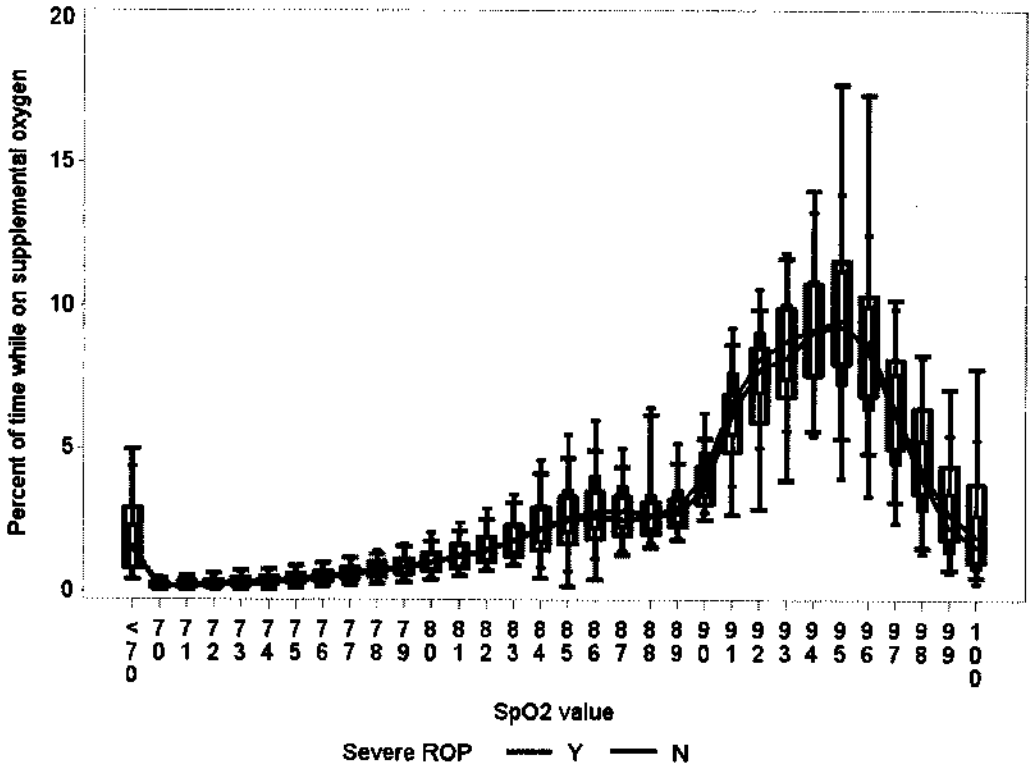


Figure 3. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination for infants who received oxygen each day (N=202)

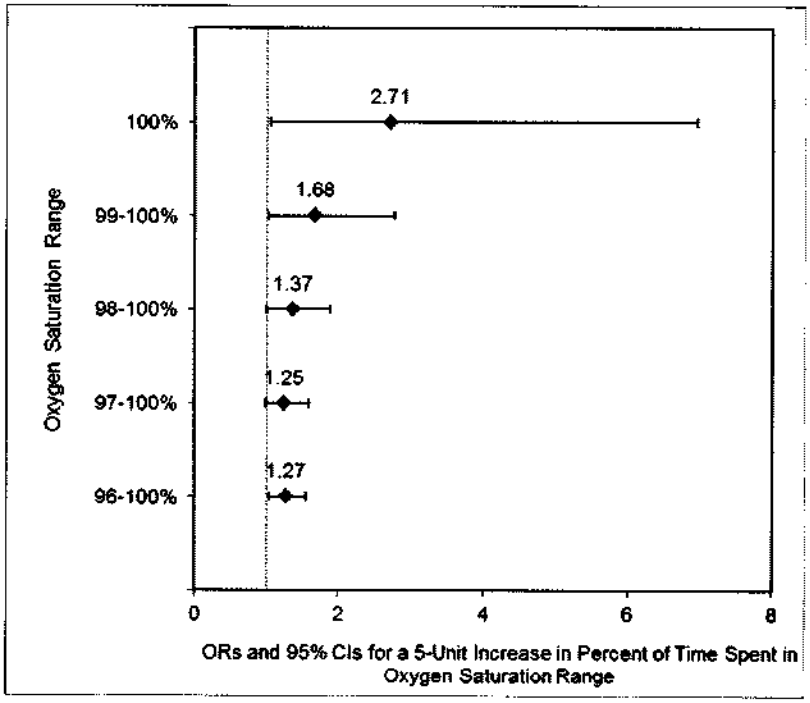


Boxes represent 25th to 75th percentiles. Whiskers represent 5th to 95th percentiles. Lines connecting the boxes represent medians.

Table. Models predicting severe ROP among survivors to discharge

	Model for all survivors to discharge			Model for survivors who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome		
	Adjusted OR	Adjusted 95% CI	P value	Adjusted OR	Adjusted 95% CI	P value
Percent of days on oxygen (unit=5% increase)	1.14	(1.06 – 1.22)	<0.001			
Percent of time with SpO2<80% (unit=5% increase)	1.03	(0.68 – 1.56)	0.89			
Percent of time with SpO2=100% (unit=5% increase)				2.71	(1.05 – 6.96)	0.04
Severe illness	3.50	(2.05 – 5.97)	<0.001	2.48	(1.04 – 5.90)	0.04
Time weighted CO_2 in the first 14 days of life	0.99	(0.95 – 1.03)	0.60			
PVL	2.09	(0.83 – 5.28)	0.12			
IVH grade 3-4	1.10	(0.53 – 2.28)	0.79			
NEC	1.11	(0.53 – 2.30)	0.78			
Late-onset sepsis or meningitis	2.11	(1.31 – 3.39)	0.002	2.31	(1.13 – 4.72)	0.02
Any antenatal steroids	0.49	(0.13 – 1.92)	0.31			
Male	1.23	(0.77 – 1.96)	0.38	2.38	(1.13 – 5.00)	0.02
Gestational age (weeks)	0.49	(0.38 – 0.63)	<0.001	0.45	(0.30 – 0.68)	<0.001
Small for gestational age	2.38	(1.04 – 5.47)	0.04	4.06	(1.35 – 12.23)	0.01
Race/ethnicity (vs. Non-Hispanic White)			0.21			
Non-Hispanic Black	0.54	(0.30 – 0.99)				
Hispanic	0.89	(0.43 – 1.84)				
Other	1.16	(0.35 – 3.82)				
Center			0.15			

Figure 4. The effect of time spent in various oxygen saturation ranges in models predicting severe ROP among survivors to discharge who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome



From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: *****Steering committee call - urgent June 11 3 PM***
Date: Tuesday, June 11, 2013 2:25:46 AM

Rose
Please resend me the numbers for me to try to call from (b)(6)
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 10, 2013 5:03 PM
To: richard.ehrenkranz@yale.edu; Finer, Neil; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org)
Subject: *****Steering committee call - urgent June 11 3 PM***
Importance: High

Hi
We will have an urgent steering committee call tomorrow at 3 PM to discuss a SUPPORT request that RTI, Dr. Carlo and Dr. Finer have received. Abhik will send the request.

Call in information:

Tues. June 11 at 3 PM ET

(b)(6) with pass code

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH

6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: GDB Early Bird PAS Proposals Conference Call (6/11, Tues, 1PM ET)
Date: Tuesday, June 11, 2013 1:28:16 PM

Sorry, my cell phone dropped the call and now it is dead. Not sure what happened. Will call you

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 11, 2013 12:16 PM
To: Wally Carlo, M.D.; Lewis-Evans, Amanda; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; Bethany Ball; Das, Abhik; Gantz, Marie; Hale, Ellen; mcw3@cwru.edu; nancy newman; Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wallace, Dennis
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: GDB Early Bird PAS Proposals Conference Call (6/11, Tues, 1PM ET)

This was cancelled and is being rescheduled
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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6100 Executive Blvd., Room 4B03
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 1:15 PM
To: Lewis-Evans, Amanda; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; Bethany Ball; Das, Abhik; Gantz, Marie; Hale, Ellen; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; nancy newman; Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu;

vanmeurs@leland.stanford.edu; Wallace, Dennis
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: GDB Early Bird PAS Proposals Conference Call (6/11, Tues, 1PM ET)

Is this call still on?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Lewis-Evans, Amanda [mailto:alewis@rti.org]
Sent: Tuesday, May 28, 2013 12:45 PM
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; Bethany Ball; Das, Abhik; Gantz, Marie; Hale, Ellen; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@cwru.edu; nancy newman; Pablo.Sanchez@UTSouthwestern.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]; Becky Brazeel; Brenda Vecchio; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; jwaidne@emory.edu; lmoore@med.wayne.edu; Zaterka-Baxter, Kristin; alewis@rti.org
Subject: RE: GDB Early Bird PAS Proposals Conference Call (6/11, Tues, 1PM ET)

Please also find the evaluation form attached.

From: Lewis-Evans, Amanda
Sent: Tuesday, May 28, 2013 1:11 PM
To: [SCRN] Stoll, Barbara (barbara_stoll@oz.ped.emory.edu); Abbot Laptook (alaptook@WIHRI.org); Bell, Edward; Bethany Ball; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); Hale, Ellen; 'Higgins, Rosemary (NIH/NICHD) [E]'; mcw3@cwru.edu; nancy newman; Pablo.Sanchez@UTSouthwestern.edu; 'sshankar@med.wayne.edu'; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.
Cc: 'Archer, Stephanie (NIH/NICHD) [E]'; Becky Brazeel; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; 'jwaidne@emory.edu'; Lewis-Evans, Amanda; 'lmoore@med.wayne.edu'; Zaterka-Baxter, Kristin
Subject: GDB Early Bird PAS Proposals Conference Call (6/11, Tues, 1PM ET)

Hi All,

The call to review the early bird PAS proposals (listed below) and additional analysis for the Mirza study is scheduled for:

Tuesday, 6/11
1:00 pm ET

Dial:
Within the USA: (b)(6)
or
Outside the USA
Then, enter Participant Passcode: (b)(6)

PROPOSALS FOR DISCUSSION

- Chawla - Neurodevelopmental Outcomes of Extremely Premature Infants Exposed to Antenatal Steroids
- Foglia - Is there a Protective Effect of Neonatal Participation in a Randomized Clinical Trial?
- Jensen - Outcomes of Extremely Low Birth Weight Infants After Gastric Fundoplication
- Natarajan - Rates, Outcomes and Predictors of Limitation of Life-sustaining therapies in the NICU
- Riehl –withdrawal outcome study
- Zhang - Prolonged Respiratory Support

Thank you,

Amanda

From: Lewis-Evans, Amanda
Sent: Wednesday, May 15, 2013 3:06 PM
To: bvohr@wihri.org; 'srhintz@stanford.edu'; Andi Duncan; Patrick Jones (Patrick.M.Jones@uth.tmc.edu); Roy.Heyne@utsouthwestern.edu; apappas@med.wayne.edu; Das, Abhik; Newman, Jamie; (b)(6) @aol.com; 'bbatton@siumed.edu'; Bradley Yoder; Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kwatterberg@salud.unm.edu; Li, Lei; 'Matt Laughon'; mcw3@cwru.edu; nancy newman; Roger.Faix@hsc.utah.edu; Wallace, Dennis; [SCRN] Stoll, Barbara (barbara_stoll@oz.ped.emory.edu); Abbot Laptook (alaptook@WIHRI.org); Bell, Edward; Bethany Ball; Hale, Ellen; Pablo.Sanchez@UTSouthwestern.edu; 'sshankar@med.wayne.edu'; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.
Cc: Cunningham, Meg; Gabrio, Jenna; Lewis-Evans, Amanda; 'Archer, Stephanie (NIH/NICHD) [E]'; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Becky Brazeel; 'Brenda Vecchio'; 'jwaidne@emory.edu'; 'lmoore@med.wayne.edu'
Subject: Early Bird PAS Proposals Discussions - Availability Request

Hi folks,

We would like to schedule 3 conference calls for the GDB, Early BP, and FU Protocol Dev subcommittees to discuss Early Bird PAS proposals.

Please provide your availability for the following dates via email or Doodle poll (link below).

Doodle Poll Link: http://doodle.com/dss7zme9asve4q4e

5/28, Tu
5/29, W
5/30, Th

5/31, F

6/3, M
6/4, Tu
6/5, W
6/6, Th
6/7, F

6/10, M
6/11, Tu
6/12, W
6/13, Th
6/14, F

6/17, M
6/18, Tu
6/19, W
6/20, Th
6/21, F

Thanks,

Amanda

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: RE: Correspondence re: Your New England Journal of Medicine Article
Date: Tuesday, June 11, 2013 11:18:52 AM

Ok

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 11, 2013 10:18 AM
To: Wally Carlo, M.D.; Finer, Neil
Subject: RE: Correspondence re: Your New England Journal of Medicine Article

Sure- bring it up on the call.

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, June 11, 2013 11:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: FW: Correspondence re: Your New England Journal of Medicine Article

Hi Rose and Neil:

This just came in. I think we should respond because NEJM is asking us to but we need to think of what we should say as it is not directly related to SUPPORT.

Should we bring this up during the call? Indeed, the NRN could develop a parent group.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

-----Original Message-----
From: onbehalfof+letter+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+letter+nejm.org@manuscriptcentral.com] On Behalf Of letter@nejm.org
Sent: Tuesday, June 11, 2013 10:09 AM
To: Wally Carlo, M.D.
Subject: Correspondence re: Your New England Journal of Medicine Article

Dear Dr. Carlo:

The attached correspondence regarding your recent article is under consideration for possible publication in a forthcoming issue. We would like to give you the opportunity to reply to the two (2) letters in print, with the stipulations that your reply not exceed 350 words of text and five references, and that we receive your letter within two weeks. Replies are subject to editing.

Your reply is due at the Journal by June 25. Notify the editorial office immediately via email to letter@nejm.org if you do not intend to respond.

Please understand that we will not make decisions regarding possible acceptance of the letters until after we receive your reply.

No more than three persons may be listed as authors of your reply.

You should inform us in your covering letter if you or any co-authors have any financial relationships with any company whose products are mentioned in the letter or a company making a competing product. Please include any new relationships that may have developed since the publication of your manuscript.

Should your letter be accepted, there should be no announcements or news releases about your letter until the day before the date of publication.

If there are any questions about these policies, you should call to discuss them.

To submit your reply, please visit http://authors.nejm.org and log in. Your case-sensitive USER ID is wcarlo@peds.uab.edu. For security purposes your password is not listed in this email. If you are unsure of your password you may click the link below to set a new password.

http://mc05.manuscriptcentral.com/nejm?URL_MASK=RqjwPqfMtrtMBNMTnhSs

Once you are logged in, the Main Menu will be displayed. Please click on the Author Center, where you will find the reply letter listed under "Invited Manuscripts." You can click on the "Continue Submission" button to begin submitting your reply letter.

Thank you for your interest in the Journal.

Sincerely,

Joe Piccirillo
Manager of Editorial Systems Workflow
New England Journal of Medicine
617.487.6587: Direct
617.739.9864: Fax

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
http://www.nejm.org

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: FW: Correspondence re: Your New England Journal of Medicine Article
Date: Tuesday, June 11, 2013 11:16:10 AM
Attachments: Letters to the Editor.pdf

Hi Rose and Neil:

This just came in. I think we should respond because NEJM is asking us to but we need to think of what we should say as it is not directly related to SUPPORT.

Should we bring this up during the call? Indeed, the NRN could develop a parent group.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

-----Original Message-----
From: onbehalfof+letter+nejm.org@manuscriptcentral.com
[mailto:onbehalfof+letter+nejm.org@manuscriptcentral.com] On Behalf Of letter@nejm.org
Sent: Tuesday, June 11, 2013 10:09 AM
To: Wally Carlo, M.D.
Subject: Correspondence re: Your New England Journal of Medicine Article

Dear Dr. Carlo:

The attached correspondence regarding your recent article is under consideration for possible publication in a forthcoming issue. We would like to give you the opportunity to reply to the two (2) letters in print, with the stipulations that your reply not exceed 350 words of text and five references, and that we receive your letter within two weeks. Replies are subject to editing.

Your reply is due at the Journal by June 25. Notify the editorial office immediately via email to letter@nejm.org if you do not intend to respond.

Please understand that we will not make decisions regarding possible acceptance of the letters until after we receive your reply.

No more than three persons may be listed as authors of your reply.

You should inform us in your covering letter if you or any co-authors have any financial relationships with any company whose products are mentioned in the letter or a company making a competing product. Please include any new relationships that may have developed since the publication of your manuscript.

Should your letter be accepted, there should be no announcements or news releases about your letter until the day

before the date of publication.

If there are any questions about these policies, you should call to discuss them.

To submit your reply, please visit http://authors.nejm.org and log in. Your case-sensitive USER ID is wcarlo@peds.uab.edu. For security purposes your password is not listed in this email. If you are unsure of your password you may click the link below to set a new password.

http://mc05.manuscriptcentral.com/nejm?URL_MASK=RqjwPqfMtrtMBNMTnhSs

Once you are logged in, the Main Menu will be displayed. Please click on the Author Center, where you will find the reply letter listed under "Invited Manuscripts." You can click on the "Continue Submission" button to begin submitting your reply letter.

Thank you for your interest in the Journal.

Sincerely,

Joe Piccirillo
Manager of Editorial Systems Workflow
New England Journal of Medicine
617.487.6587: Direct
617.739.9864: Fax

New England Journal of Medicine
10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
http://www.nejm.org

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, June 10, 2013 2:31 PM
To: Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: FR notice re SUPPORT public meeting
Attachments: SUPPORT public meeting FR notice 6.5.13.doc

Fyi.... Weird that it still doesn't have a date and thus hasn't been put into fed reg process....

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 10, 2013 2:14 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FR notice re SUPPORT public meeting

This is the final sent to OHRP

DEPARTMENT OF HEALTH AND HUMAN SERVICES

[Docket No. xxxxx]

HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions; Notice of Meeting

AGENCY: Department of Health and Human Services.

ACTION: Notice of meeting; request for comments.

SUMMARY: The Department of Health and Human Services (HHS) is announcing a public meeting to discuss how certain provisions of the HHS protection of human subjects regulations, 45 CFR part 46, should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically is requesting input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process.

HHS is seeking participation in the meeting and written comments from all interested parties, including, but not limited to, IRB members, IRB staff, institutional officials, research institutions, investigators, research subject advocacy groups, ethicists, and the regulated community at large. This meeting and the written comments are intended to assist HHS, through the Office for Human Research Protections (OHRP), Office of the Assistant Secretary for Health (OASH), in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects. HHS is seeking input on a number of specific questions but is interested in any other pertinent information participants in the public meeting would like to share.

DATES AND TIMES: The public meeting will be held on August xx, 2013, from 9 a.m. to 5 p.m.

Deadline for Registration for Participants (not Presenting) at the Public Meeting and Submitting Requests for Special Accommodations: The deadline to register to attend the public meeting and requests for special accommodations must be received no later than 5:00 p.m. on August 14, 2013.

Deadline for Registration of Presenters at the Public Meeting: The deadline to register to present at the public meeting must be received no later than 5:00 p.m. on August 7, 2013.

Deadline for Submission of Written Comments for the Public Meeting: Written comments for discussion at the public meeting must be received by August 7, 2013. In addition to materials submitted for discussion at the public meeting, individuals may submit other written comments after the public

meeting, as specified in the ADDRESSES section of this notice. These comments must be received by September 9, 2013, for consideration by HHS.

ADDRESSES: *Meeting Location:* The Public Meeting will be held at the Department of Health and Human Services, Hubert H. Humphrey Building, 200 Independence Ave. SW, Room 800, Washington, DC 20201; Metro: Federal Center SW station.

In addition, we are providing two alternatives to attending the meeting in person–(1) there will be an open toll-free phone line to call into the public meeting; or (2) participants may view the public meeting via live streaming technology. Information on these options is provided in section II.D. of this notice.

Registration and Special Accommodations: While there is no registration fee, individuals planning to attend the public meeting in person must register to attend. Registration may be completed by sending an email to OHRP@hhs.gov, with the subject line "Registration for HHS Public Meeting"; or a request to register may be sent to Registration for HHS Public Meeting, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200; Rockville, MD 20852. Please include your name, address, telephone number, email address and fax number. If you would like to present at the public meeting, please state this in the registration submission.

Registration to attend the public meeting will be accepted on a first-come, first-served basis. If seating capacity has been reached, you will be notified that the meeting has reached capacity.

Registration to present at the public meeting will be accepted on a first-come, first-served basis. HHS has included questions for comment in section III of this document. Please identify by number each question you wish to address in your presentation and the approximate time requested. HHS will do its best to accommodate requests to speak. HHS will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin. Once HHS notifies registered presenters of their scheduled times, presenters should submit to a copy of each presentation, identified with docket number HHS-OPHS-2013-0004, to http://www.regulations.gov.

Individuals who need special accommodations should contact staff listed in the FOR FURTHER INFORMATION CONTACT section of this notice.

Submission of Comments for the Public Meeting:

Submit electronic comments, identified with docket number HHS-OPHS-2013-0004, to http://www.regulations.gov.

Submit written comments to Comments for HHS Public Meeting, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200; Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dr. Jerry Menikoff, Director, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200; Rockville, MD 20852, 240-453-6900; email Jerry.Menikoff@hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

A. HHS Protection of Human Subjects Regulations

HHS, through OHRP, regulates research involving human subjects conducted or supported by HHS in regulations codified at 45 CFR part 46. The HHS protection of human subjects regulations identify requirements that pertain to several different entities, including the IRB charged with reviewing non-exempt human subjects research.

The IRB is an administrative body that takes the form of a board, committee, or group, and is responsible for conducting the initial and continuing review of research involving human subjects. The IRB must have authority to approve, require modification in (in order to secure approval), or disapprove all research activities covered by the HHS regulations (45 CFR 46.109(a)). An IRB's primary purpose in reviewing research is to ensure the protection of the rights and welfare of human research subjects. In order to approve research, an IRB is required to make certain determinations, including that the following criterion is met for the research under review (45 CFR 46.111(a)(2)):

> Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

The HHS protection of human subjects regulations further require that, unless this requirement is waived by the IRB, an investigator must obtain informed consent from research subjects prior to the subjects' participation in the research, and that, in this informed consent process, the subjects must be provided "a description of any reasonably foreseeable risks or discomforts to the subject" (45 CFR 46.116(a)(2)).

B. OHRP's Compliance Oversight Investigation of SUPPORT

On March 7, 2013, OHRP issued a compliance oversight determination letter regarding its investigation into "The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" (SUPPORT) clinical trial (http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf), in which OHRP determined that certain risks related to the interventions being studied in the SUPPORT trial were required by the HHS protection of human subjects

regulations to be disclosed to the research subjects, and the subjects were not informed of these risks. OHRP's view of the SUPPORT trial, as described in this determination letter, triggered extensive public discussions regarding (1)what risks to subjects are presented by clinical trials studying interventions that are standard of care in the clinical treatment context, such that an IRB must evaluate those risks in relation to the anticipated benefits of the research as required by 45 CFR 46.111(a)(2); and (2)how an IRB should assess whether those risks are reasonably foreseeable such that the risks must be described to subjects in informed consent as required by 45 CFR 46.116(a)(2). Through the public reaction to OHRP's determination letter, HHS has become aware of differing perspectives in the scientific, research, and ethics communities about these issues and how the relevant requirements of the HHS protection of human subjects regulation should apply to research studying standard of care interventions.

II. Public Meeting

A. Purpose and Scope of the Meeting

The public meeting is intended to provide an opportunity for broad public participation and comment concerning how the requirements of the HHS protection of human subjects regulations, 45 CFR part 46, should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically is requesting input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one of more standard of care interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. This meeting and the written comments are intended to assist HHS, through the Office for Human Research Protections (OHRP), Office of the Assistant Secretary for Health (OASH), in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects.

While HHS is considering whether other processes should be incorporated into OHRP's compliance oversight procedures and guidance, including, but not limited to, consultation with subject matter experts during the course of a compliance oversight investigation, and an administrative process for appealing OHRP determinations of noncompliance, please note that this meeting is not intended to specifically address possible revisions to OHRP's compliance oversight procedures.

B. Format of the Meeting

The meeting will be conducted by a panel of HHS officials, including the Director of OHRP. The majority of the meeting will be reserved for presentations of comments, recommendations, and data from registered presenters. The time for each presenter's comments will be determined by HHS and will be based on the number of registered presenters. Presenters will be scheduled to speak in the order in which they register. Only the HHS panel members may question any presenter during or at the conclusion of each presentation. The meeting will be recorded and transcribed.

In addition, written comments will also be accepted and presented at the meeting, time permitting, if they are received by the date specified in the DATES section of this notice.

Only the HHS panel members may question any presenter during or at the conclusion of each presentation.

C. Security and Building Guidelines

Because the public meeting will be located on Federal property, for security reasons, any persons wishing to attend these meetings must register by the date specified in the DATES section of this notice. Please allow sufficient time to go through the security checkpoints. It is suggested that you arrive at the Hubert H. Humphrey Building no later than 8:30 a.m. if you are attending the public meeting.

Security measures include the following:

- Presentation of government-issued photographic identification to the Federal Guard Service personnel.
- Passing through a metal detector and inspection of items brought into the building. We note that all items brought to HHS, are subject to inspection.

Note: Individuals who are not registered in advance will not be permitted to enter the building and will be unable to attend the meeting in person. The public may not enter the building earlier than 45 minutes prior to the convening of the meeting(s). All visitors must be escorted while in the building.

D. Conference Call and Live Streaming Information

For participants who cannot attend the public meeting in person, an open toll-free phone line will be made available. The call-in number and the conference code will be posted on the OHRP website, http://www.hhs.gov/ohrp, prior to the public meeting.

Also, there will be an option to view the public meeting via live streaming technology. Information on the option to view the meeting via live streaming technology will be posted at a later time on the OHRP website at http://www.hhs.gov/ohrp. Please continue to check the OHRP website for updates.

III. Issues for Discussion

Questions have arisen regarding the application of the HHS protection of human subjects regulations to research studying one or more interventions which are provided as standard of care treatment in the non-research context. HHS invites comment at the public meeting about how an IRB should assess the risks of research involving randomization to one of more standard of care interventions, and what risks of the research should be disclosed to research subjects in the informed consent process. HHS is specifically interesting in public input on the following questions:

1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?
   a. Under what circumstances should an IRB consider those risks that may result from the research?
   b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?
   c. What type of evidence should an IRB evaluate in identifying these risks?

2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects?
   a. What criteria should be used by the IRB to evaluate whether the risks to subjects are reasonably foreseeable?

3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk? Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?

4. How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions? What if the risk significantly varies within the standard of care?

5. Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases the risk of harm or is it necessary that there be published studies identifying the risk?

IV. Transcripts

As soon as a transcript of the public meeting is available, it will be accessible on the OHRP website, http://www.hhs.gov/ohrp. A transcript also will be available in either hardcopy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to the PHS FOIA Office, 7700 Wisconsin Avenue, Suite #920, Bethesda, MD 20857; telephone (301)492-4800; fax(301)492-4848; email FOIARequest@psc.hhs.gov.

Dated: June 5, 2013.

Howard K. Koh
Assistant Secretary for Health

BILLING CODE xxxxx

From: Ehrenkranz, Richard
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: *****Steering committee call - urgent June 11 3 PM***
Date: Monday, June 10, 2013 12:14:27 PM

Thanks. I have a meeting scheduled for 3:30 and will try to move it to 4 pm.
Richard

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 10, 2013 11:58 AM
To: Ehrenkranz, Richard
Subject: RE: *****Steering committee call - urgent June 11 3 PM***

Not sure but we are allocating 1 hour
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Monday, June 10, 2013 11:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: *****Steering committee call - urgent June 11 3 PM***

Rose:
How long will this call last? 30 min or 60 min?
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

recipient, you must maintain this message in a secure and confidential manner. If you are not the intended recipient, please notify the sender immediately and destroy this message. Thank you.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 10, 2013 11:03 AM
To: Ehrenkranz, Richard; nfiner@ucsd.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org)
Subject: *****Steering committee call - urgent June 11 3 PM***
Importance: High

Hi
We will have an urgent steering committee call tomorrow at 3 PM to discuss a SUPPORT request that RTI, Dr. Carlo and Dr. Finer have received. Abhik will send the request.

Call in information:

Tues. June 11 at 3 PM ET

(b)(6) with pass code

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575

301-496-3790 (FAX)
higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 12:01 PM
To: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]
Subject: FW: *****Steering committee call - urgent June 11 3 PM***
Attachments: public citizen apra request and response.pdf

We have sent up a steering committee call to discuss the request from Public Citizen for the SUPPORT data set. See correspondence below from a few of the PI's

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]
Sent: Monday, June 10, 2013 11:33 AM
To: 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wacarlo@uab.edu
Subject: RE: *****Steering committee call - urgent June 11 3 PM***

Abhik,
Attached is the document that our legal counsel sent to Public Citizen. I forwarded the letter from Public Citizen to RTI asking for the data to our legal counsel; he has been incredibly helpful so I wanted to see if he has any thoughts about this – my guess is that he will strongly say that the request made is not consistent with applicable FOIA disclosure requirements. I'll let you know what he has to say.
Brenda

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, June 10, 2013 11:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Bradley.yoder@hsc.utah.edu; dale_phelps@urmc.rochester.edu; Frantz, Ivan; EMcGowan@tufts-nemc.org; SDuara@med.miami.edu; moshea@wfubmc.edu; suhas.kallapur@cchmc.org; alaptook@wihri.org; ambal@uab.edu; AnnaMaria.hibbs@cwru.edu; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; Wallace, Dennis; edward-bell@uiowa.edu; goldb008@mc.duke.edu; gsokol@iupui.edu; KIRPALANIH@email.chop.edu; John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; vanmeurs@stanford.edu; kwatterberg@salud.unm.edu; kurt.schibler@cchmc.org; luc.brion@utsouthwestern.edu; mkeszler@wihri.org; mcw3@po.cwru.edu; mgarg@mednet.ucla.edu; Nelin, Leif; Pablo.Sanchez@utsouthwestern.edu; Polin, Richard; rohls@salud.unm.edu; ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; bsood@med.wayne.edu; Truog, William (MD);

UDEVASKAR@mednet.ucla.edu; wacarlo@uab.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin
Subject: RE: *****Steering committee call - urgent June 11 3 PM***

Hello All:

Here is the communication we received from Public Citizen that is necessitating this call. There are a few issues to consider here:

1. We have 6-7 year follow up for the trial ongoing and we typically have no plans to make any data public before follow up closes and the results are published. The last visit window for this follow up closes in April 2016. In addition, the request also asks for GDB data (eligible but not enrolled in SUPPORT), which has always been considered an ongoing study not subject to NIH data sharing policies.

2. RTI is the custodian, and not the owner of NRN data. The data belongs to the steering committee, and so I think it is ultimately not our decision as to whether or how it should be released. We will follow the direction of the NRN and NICHD on this matter.

3. The preliminary read of RTI legal counsel is that RTI is not subject to FOIA and we are not under any obligation to respond to this communication or release study data to third parties without a court subpoena. That being said, they think it is virtually certain that such a request/order from a court will come as a result of ongoing litigations and we should be ready with a plan to respond.

4. SUPPORT is a very complex trial with a huge amount of data coming from multiple sources (trial forms, GDB forms, pulse oximeter readings, follow up forms, etc.), and will require an extra-ordinary amount of detailed documentation to accompany any data release for it to be usable to groups not well versed with neonatal trials. Clearly, what they are asking for would require very significant resources at RTI to comply, if we were to allow this request.

I have also pasted below for your reference the data sharing plan that RTI had in our latest DCC grant application to NIH.

15.1 Data Sharing Plan

Based on our past experience as DCC for the NRN, RTI realizes the importance of sharing resources, including protocols, manuals, training materials, and study data with researchers and other members of the public. We will continue to work with the NRN Steering Committee and the NICHD to develop and implement plans for resource sharing, while maintaining acceptable levels of patient confidentiality. Upon approval from the NICHD and the Network Steering Committee, we have shared study materials (e.g., protocols, manuals, training materials, CRFs that are not copyrighted by other organizations) through annotated CD-ROMs distributed by RTI or NICHD, by preparing materials for release by a resource warehouse, by e-mail response to individual requests, and by posting materials to a public or private website. In some cases, these materials have been openly available to the public. In other cases, the Steering Committee has limited release of some of these materials, and RTI staff will abide by guidelines adopted by the NRN to implement the limitations set by agreement of the Steering Committee. RTI will continue to work with the Steering Committee and NICHD to develop plans for release of study materials.

The data collected through NRN DCC have and will continue to provide a wealth of information regarding disease in neonates with the potential for translating these findings to practice. As the DCC, RTI will be responsible for working with NICHD, the Steering Committee, and the clinical centers to develop a plan and schedule for distributing this valuable resource to both internal and external researchers. The plan for sharing the Network data demands a carefully developed strategy that is cognizant of the importance of protecting participants' rights to individual privacy and is compliant with HIPAA regulations and other compliance requirements.

The DCC will assist in preparing de-identified data files for sharing if approved by NICHD, and the Steering Committee. Shared data can be aggregated at the individual study center level, aggregated as micro data with no identifiers, or aggregated as micro data with one or more identifiers. Data may also be shared at several levels: with Investigators at Network institutions and with outside Investigators. Each level of aggregating and

sharing data carries its own level of disclosure risk. Data sharing plans should be developed for each protocol before implementation so that risks related to data release can be explained to the patient when informed consent is obtained.

RTI will take great care to ensure that participant confidentiality is maintained in all shared data. Several options to protect privacy of the data include releasing only part of the data, altering the data in ways that will not compromise analyses, requiring outside researchers to adhere to strict confidentiality requirements, or providing access to the data through a controlled data enclave. Because of the inclusion of potentially sensitive outcomes, the best release option may be to create limited data set agreements (LDA) for public release that satisfy all HIPAA and any related international requirements for protecting participant identity. RTI has experience in producing LDA that conform to both HIPAA requirements and NIH policy on data sharing (see ***Appendix 13*** for a template). As the DCC, RTI will continue to work within established regulatory guidelines to develop and implement procedures for the NRN to release restricted or public-use data sets. Two recent examples include

- The development of an Anonymized DNA Bank linked to phenotype data for extremely low birth weight infants derived from the NRN's Cytokines Study that enrolled extremely low birth weight infants (<1000 grams at birth) between 1998 and 2001 and collected serial filter card blood spot samples during the first postnatal weeks.[63] The blood spots and extracted DNA are included in the NRN's DNA bank maintained at the Duke University Center for Human Genetics. The enrolled patients had 3 years of clinical and outcome data entered into the NRN database maintained at RTI. Those data, stripped of dates and other identifiers, comprise the anonymized database linked to the samples. Initial association studies, including a GWA study funded by NHGRI GENEVA grant (NHGRI: HG 4423) are underway. GWA study data are now linked to the anonymized database at RTI, and genotype and phenotype data have been prepared for sharing in the National Center for Biotechnology Information (NCBI) database of genotypes and phenotypes (dbGaP).
- Upon approval by the Steering Committee, data was shared with the University of Texas Health Science Center at Houston for specialized Bayesian secondary analysis from the NRN Randomized trial of Aggressive of Conservative Phototherapy for Extremely Low Birth weight Infants.

Data Sharing with NRN Investigators. The first level of data sharing will be with multiple NRN Investigators. NRN clinical centers will continue to complete the DCC's Annual Data Access Agreement to receive their own center's cleaned and edited GDB and Follow-up registry data. Centers can stipulate the format in which they would like to receive their data by completing the Data Request Form, which must be submitted to the DCC in addition to the Agreement. This agreement allows the Network to track and confirm that centers request and receive their data each year. The necessary forms are located on the NICHD NRN website.

Some centers may request a Data Use Agreement between the DCC and the clinical center, primarily for studies such as the GDB that are conducted under waiver of consent in many centers, to ensure all entities involved in the data collection for research purposes, to their fullest ability, respect the confidentiality and protection of personal health information. If the study is conducted under consent, the consent process usually addresses HIPAA requirements and includes indemnification clauses.

Once data from an NRN study have been cleaned and locked, and preliminary analyses indicate that the data are ready to be shared on a rolling basis among the NRN researchers, data files containing each clinical center's data can be released to the investigators at that center by posting the data on the secure portion of the NRN website or distributing it on CD as determined in collaboration with the Steering Committee. Appropriate documentation will be provided including labeled versions of CRFs, raw data sets, edited analysis data sets, format files for variables, and data dictionaries. The data can be provided in SAS data sets and export files and documentation will be in PDF format. These files can be developed on a periodic basis determined by the Steering Committee, for instance, 6 months after locked data sets for the study have been prepared for final analysis or 1 month after results of the study are published in a peer-reviewed journal.

The purpose of granting limited access is for researchers to develop appropriate analysis approaches and identify preliminary indications of findings using their own center data. Investigators will be able to participate in distributed data analysis using patient-level data collected at their centers, but the DCC will be responsible for conducting statistical analyses and producing summary reports of all study-wide data. Steering Committee permission will be required for investigators to gain access to patient-level data collected at other centers before de-identified, limited-access data sets can be disseminated.

Data Sharing with the Broader Research Community. In addition to internal data sharing, the DCC will be responsible for sharing study data with outside researchers, if approved by the NRN Steering Committee,

and NICHD. De-identified limited-access data sets will be created for this purpose. Although the data sets will be stripped of identifiers and otherwise modified to prevent easy identification of patients in the study, the narrow focus of the population to be analyzed and the possible rarity of some outcome measures and risk factors might make it possible for an identification to be made. To protect the confidentiality and privacy of the subjects, investigators granted access to these data must adhere to strict requirements. The Steering Committee will define these requirements and establish criteria for access to data by outside researchers. This information will be incorporated into a standard Data Distribution Agreement to which investigators must adhere. The agreement will be subject to review by legal and IRB departments of RTI and the clinical centers, and approved by the Steering Committee. In accordance with NICHD policies, outside researchers will be required to submit an approval from their IRB.

Thanks

Abhik

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 10, 2013 11:03 AM
To: richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Das, Abhik; Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); [SCRN] Stoll, Barbara; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; Wallace, Dennis; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org);

mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin
Subject: *****Steering committee call - urgent June 11 3 PM***
Importance: High

Hi
We will have an urgent steering committee call tomorrow at 3 PM to discuss a SUPPORT request that RTI, Dr. Carlo and Dr. Finer have received. Abhik will send the request.

Call in information:

Tues. June 11 at 3 PM ET

(b)(6) with pass code

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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INDIANA UNIVERSITY
OFFICE OF THE VICE PRESIDENT
AND GENERAL COUNSEL

May 15, 2013

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group
PUBLIC CITIZEN
1600 20th Street, NW
Washington, DC 20009

Re: Open Records Request

Dear Dr. Carome:

I write to acknowledge receipt of your request for records, dated May 13, 2013, directed to the Indiana University Office of Research Administration in Indianapolis requesting the following documents:

1. The initial and continuing review applications for the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT study; ClinicalTrials.gov number NCT00233324) that were submitted to the Indiana University (IU) institutional review board (IRB).

2. The minutes of any IU IRB meetings related to the initial and continuing review and/or approval of the SUPPORT study.

3. The initial and continuing review applications for the Transfusion of Prematures (TOP) Trial: Does a Liberal Red Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compares to a Restrictive Strategy (TOP study; ClinicalTrials.gov number NCT01702805) that were submitted to the IU IRB.

4. All versions of the consent/parental permission forms for the TOP study that were approved by the IU IRB.

5. The minutes of any IU IRB meetings related to the initial and continuing review and/or approval of the TOP study.

Indiana's Access to Public Records Act ("APRA") specifically exempts certain records from disclosure, including "...information concerning research, including actual research

Fairbanks Hall 340 W. 10th Street Suite 5100 Indianapolis, IN 46202-3082 (317) 274-7460 fax (317) 231-2124
Indiana University–Purdue University Indianapolis

documents, conducted under the auspices of an institution of higher education, including information (A) concerning any negotiations made with respect to the research; and (B) received from another party involved in the research." (Indiana Code 5-14-3-4(a)(6)) See also Robinson vs. Indiana University, 659 N.E. 2nd 153 (Ind. App. 1995). APRA also exempts from disclosure "records that are intra-agency or interagency advisory or deliberative material, including material developed by a private contractor under a contract with a public agency, that are expressions of opinion or are of a speculative nature, and that are communicated for the purpose of decision making." In addition, Indiana Code 5-14-3-4(a)(9) exempts from disclosure patient medical records and charts and Indiana Code 5-14-3-4(a)(3) exempts from disclosure documents subject to the protections of HIPAA or other applicable federal law.

Thus, it is the University's conclusion that the records you seek are not available under APRA.

Sincerely,

Joseph M. Scodro
Deputy General Counsel

JMS/lmk

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

May 13, 2013

John Baumann
Executive Director
Human Research Protection Program
Office of Research Administration
Indiana University
Lockefield Village, 3rd Floor
980 Indiana Avenue
Indianapolis, Indiana 46202

SENT BY EMAIL TO: baumannj@IU.edu

Dear Mr. Baumann:

On behalf of Public Citizen's Health Research Group, and pursuant to the Indiana Access to Public Records Act, Ind. Code § 5-14-1.5, I hereby request the following documents:

(1) The initial and continuing review applications for the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT study; ClinicalTrials.gov number NCT00233324) that were submitted to the Indiana University (IU) institutional review board (IRB). Please exclude from this part of the request any version of the document entitled "Protocol for the NICHD Neonatal Research Network - The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants - The SUPPORT Trial" because this document has been made publicly available by the National Institutes of Health.

(2) The minutes of any IU IRB meetings related to the initial and continuing review and/or approval of the SUPPORT study. Please only provide the relevant pages that indicate the date, attendance, discussion, action and vote regarding any meetings related to the initial or continuing review of the SUPPORT study.

(3) The initial and continuing review applications for the Transfusion of Prematures (TOP) Trial: Does a Liberal Red Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to a Restrictive Strategy (TOP study; ClinicalTrials.gov number NCT01702805) that were submitted to the IU IRB.

(4) All versions of the consent/parental permission forms for the TOP study that were approved by the IU IRB.

(5) The minutes of any IU IRB meetings related to the initial and continuing review and/or approval of the TOP study. Please only provide the relevant pages that indicate the date, attendance, discussion, action and vote regarding any meetings related to the initial or continuing review of the TOP study.

Public Citizen asks that IU produce the responsive records in electronic form by e-mail (send to mcarome@citizen.org) if doing so would be less costly than standard duplication. If the University determines that fulfillment of this request would nevertheless result in the assessment of fees, Public Citizen seeks a discretionary waiver of those fees.

Public Citizen, which has 300,000 members and supporters, is a nonprofit research, litigation, and advocacy organization that represents the public interest before federal and state legislatures, executive branches, and the courts. It fights for openness and democratic accountability in government; for social and economic justice in globalization and trade policies; for strong health, safety, human subjects and environmental protections; and for safe, effective and affordable medicines and health care. It is composed, in part, by its Health Research Group. Public Citizen intends to share information received from this request with the public. It regularly publishes reports based upon information acquired through freedom of information (FOI) requests. Public Citizen disseminates its reports via publication, through its website, and through various newsletters that are distributed to consumers, lawyers, academics, and other interested parties. Public Citizen staff members also serve as a resource for the media and testify before Congress.

We expect that the responsive records will reveal important information regarding the IU's oversight process for clinical trials. The documents being sought will allow the public to evaluate whether University of Indiana provided sufficient oversight for the SUPPORT and TOP studies, including whether the university took proper precautions to ensure the protection of human subjects. As you are probably aware, the SUPPORT study has received substantial media attention over the past several weeks.

In the event that fulfillment of this request would incur fees and a fee waiver is not granted, Public Citizen requests that the IU provide Public Citizen with an estimate of the cost of producing the records before conducting any work that would incur those costs.

If you are not the correct individual to process this public records request, please forward it immediately to the appropriate person or office and notify me of that referral action.

Thank you for your prompt attention to this request.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group
mcarome@citizen.org
(202) 588-7781

From: Bell, Edward (Pediatrics)
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: *****Steering committee call - urgent June 11 3 PM***
Date: Monday, June 10, 2013 11:46:35 AM

I missed that. Thanks.

On Jun 10, 2013, at 11:42 AM, "Das, Abhik" <adas@rti.org> wrote:

It seems footnoted in the request:

[1] National Institutes of Health. NIH Data Sharing Policy and Implementation Guidance. March 5, 2003. http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. Accessed June 6, 2013.

Thanks

Abhik

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Monday, June 10, 2013 11:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: Re: *****Steering committee call - urgent June 11 3 PM***

Rose,
Can you send us the NIH policy on data sharing referred to in the request.
Thanks,
Ed

On Jun 10, 2013, at 11:02 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

Hi
We will have an urgent steering committee call tomorrow at 3 PM to discuss a SUPPORT request that RTI, Dr. Carlo and Dr. Finer have received. Abhik will send the request.

Call in information:

Tues. June 11 at 3 PM ET

(b)(6) with pass code

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD
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Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 11:17 AM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: web page you mentioned

I would not [(b)(6)] for sharing.

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, June 10, 2013 10:45 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: web page you mentioned

I found this [(b)(6)]
Joe never reads the NEJM out loud to me... ☺d

From: Lauer, Michael (NIH/NHLBI) [E]
Sent: Friday, June 07, 2013 3:49 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: web page you mentioned

Hi Kathy – see here: http://www.ahrp.org/cms/content/view/924/9/. You may have to scroll down a ways to see the text.

It does not refer to NIH, but rather "the powerful institutions of medical research."

I read your NEJM essay [(b)(6)] is "beautifully written – considering how inflammatory the situation is it's a perfectly modulated piece." In particular, your call for OHRP to call in external experts when considering difficult cases – something, of course, that NIH does as a matter of routine through our study sections, working groups, and councils.

All best, Mike

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, June 06, 2013 10:14 PM
To: Lauer, Michael (NIH/NHLBI) [E]
Subject: web page you mentioned

Who has comments posted about support and nih role? Aahrpp? I did'nt see anything on their page.

Thanks

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:27 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

(b)(5) I think, to make sure we are (b)(5)
(b)(5)
(b)(5) So, for now, I would continue simply to follow established NRN/SUPPORT policies.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
31 Center Drive
Building 31, Room 2A03
Bethesda, MD 20892-2425

Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:20 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

One more question –Dr. Carome has requested SUPPORT data and we have 6.5-7.5 year follow up ongoing. We do not release data if a study is ongoing. This is also true for the Generic Data Base. Would there be guidance on this issue of studies which are still ongoing?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:03 AM

To: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Hi
Here are the RTI application with an extensive resource sharing policy which starts on page 118 and the NRN policies and procedures with Data Access which starts on page 37.

For data sharing (given the human subjects issues- i.e. an infant could potentially be identified by birth weight, gestational age, and center), the procedures were developed. A proposal to is sent to the appropriate subcommittee (would be SUPPORT in this case) and reviewed and then reviewed and approved by the steering committee. If approved, generally an IRB approval is required and a data use agreement is negotiated by RTI with the recipient's institution and recipient.
Let me know if there are questions.
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 7:41 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

More on the most recent info request, which did not come to us, of course (we were only cc:ed), but only to the investigators and RTI...

Alan

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, June 09, 2013 10:16 PM
To: Muroff, Julie (NIH/OD) [E]
Cc: McGarey, Barbara (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]
Subject: Re: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Thank you so much Julie. (b)(5) I guess that is why our jobs are quietly entertaining.

I am sharing via cc your opinion with pat white and Alan Guttmacher. (For reasons I do not understand my iPhone thinks Alan should be with caps but not pat.).

Alan - we look forward to response from nichd. pat, we look forward to an explanation of why your name is not capitalized.

Warmly,
Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On Jun 9, 2013, at 7:51 PM, "Muroff, Julie (NIH/OD) [E]" <muroffj@od.nih.gov> wrote:

(b)(5)

Julie A. Muroff, J.D., LL.M.
Senior Attorney
HHS Office of the General Counsel, PHD, NIH Branch
31 Center Drive, Bldg. 31, Rm.2B-47
Bethesda, MD 20892
301-451-4910 (direct)
301-402-1034 (Fax)
Julie_Muroff@nih.gov

From: McGarey, Barbara (NIH/OD) [E]
Sent: Friday, June 07, 2013 10:47 PM
To: Rockey, Sally (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

(b)(5)

From: Rockey, Sally (NIH/OD) [E]
Sent: Friday, June 07, 2013 09:58 PM
To: Hudson, Kathy (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

(b)(5)

Sally J. Rockey, Ph.D.
NIH Deputy Director for Extramural Research
OD/NIH/DHHS
One Center Drive
Building 1, Room 144
Bethesda, MD 20892
301-496-1096 (BLDG. 1)
301-435-2698 (ROCK I)
301-402-3469 Fax
rockeysa@od.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, June 07, 2013 9:29 PM
To: Rockey, Sally (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

I am thinking (b)(5)
(b)(5)
(b)(5) Do you agree?

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, June 07, 2013 5:19 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

FYI...

Alan

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 5:16 PM
To: adas@rti.org; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 9:07 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Attachments: Final Response.pdf; 130608_FOIArequest to NIH_TOP Study Review Documents_FINAL.PDF

Rose, Earl and I just met—we affirmed that this is no longer a FOIA issue. Our response to Carome for the FOIA request for patient data is attached.

Now it does become a data use policy question and since RTI is not a state institution it does not operate under the state FOIA laws as would a state academic institution. The data sharing policy from the DCC would hold sway and will leave it to the experts there.

BTW Michael Carome sent another FOIA request –this time just focusing on the TOPS trial—Earl will work with NHLBI and we talked with Rose on what will be needed to full this request – it is even broader than the other one like this as it seeks all documentation – not only (b)(5)

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 7:41 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
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Subject: Re: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

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Alan - we look forward to response from nichd. pat, we look forward to an explanation of why your name is not capitalized.

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Kathy

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(b)(5)

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(b)(5)

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Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

(b)(5)

Sally J. Rockey, Ph.D.
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(b)(5) Do you agree?

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Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

From:	Higgins, Rosemary (NIH/NICHD) [E]
To:	Rowe, Mona (NIH/NICHD) [E]
Cc:	Blansfield, Earl (NIH/NICHD) [E]
Subject:	FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date:	Monday, June 10, 2013 8:30:00 AM
Attachments:	130607_Letter to SUPPORT Study Investigators Requesting Study Data_FINAL_Signed.doc

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, June 07, 2013 5:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

-----Original Message-----
From: Michael Carome [mcarome@citizen.org]
Sent: Friday, June 07, 2013 05:15 PM Eastern Standard Time
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

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Public Citizen
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Washington, DC 20009

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Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

June 7, 2013

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
3040 East Cornwallis Road
Post Office Box 12194
Research Triangle Park, NC 27709-2194

Waldemar A. Carlo, M.D.
Director, Division of Neonatology
University of Alabama at Birmingham
Women & Infants Center
1700 6th Avenue
South Birmingham, AL 35233

Neil N. Finer, M.D.
Chief, Division of Neonatology
Department of Pediatrics
School of Medicine
University of California, San Diego
3020 Children's Way, MC 5109
San Diego, CA 92123-5109

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Drs. Das, Carlo, and Finer:

In accordance with the National Institutes of Health's (NIH's) long-standing data sharing policy,[1] which requires data sharing for all NIH-funded grants, Public Citizen's Health Research Group respectfully requests a digital copy of all individual subject-level data — without subject identifiers — obtained for the SUPPORT study that was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The data being requested includes the data on actual oxygen saturation levels that were achieved for each subject over the course of their involvement in the study. We are seeking all data for (a) the 1,316 subjects enrolled and randomly assigned to one of the four experimental groups in the SUPPORT study; and (b) those subjects who were eligible to be, but were not, enrolled in the SUPPORT study, and for whom

[1] National Institutes of Health. NIH Data Sharing Policy and Implementation Guidance. March 5, 2003. http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. Accessed June 6, 2013.

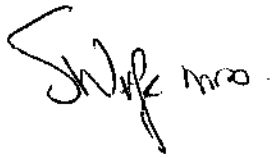
data was collected and published regarding demographics, baseline clinical characteristics, and clinical outcomes.[2]

We also respectfully request that you provide with the data (a) an explanation of the format used for storing the data; (b) a description of how the data was coded; and (c) the case report forms for each subject.

Thank you for your prompt attention to this request. Please notify us immediately if you have any questions about the data we are seeking or anticipate problems fulfilling our request.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Senior Advisor and Founder
Public Citizen's Health Research Group

cc: Dr. Allan Guttmacher, Director, National Institute of Child Health and Human Development

[2] Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics.* March 2012;129(3):480-484.

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Monday, June 10, 2013 8:28:51 AM

Thanks and no worries, I just received it too, didn't know if it came up before. I would (b)(5)

(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 8:10 AM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

No
Just got this in the last hour – will pull the policies and also the data sharing plan from the RTI application

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 8:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Rose,
Sounds like you need to provide information on the datasharing policy for the NRN – or have you already done this?
cathy

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 7:41 AM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
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More on the most recent info request, which did not come to us, of course (we were only cc:ed), but only to the investigators and RTI...

Alan

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Cc: McGarey, Barbara (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]
Subject: Re: Confidential-attorney/client communication RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Thank you so much Julie. (b)(5)
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NIH
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kathy.hudson@nih.gov

On Jun 9, 2013, at 7:51 PM, "Muroff, Julie (NIH/OD) [E]" <muroffj@od.nih.gov> wrote:

(b)(5)

Julie A. Muroff, J.D., LL.M.
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Cc: Devaney, Stephanie (NIH/OD) [E]; Muroff, Julie (NIH/OD) [E]
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

(b)(5)

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(b)(5)

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Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on

data sharing

I am thinking (b)(5)

(b)(5)

(b)(5) Do you agree?

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FYI...

Alan

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email: mcarome@citizen.org
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Monday, June 10, 2013 8:13:00 AM

RTI is putting data on clinicaltrials.gov – they were getting some error messages and Steven Hirschfeld was assisting

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 8:11 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Rose, are you planning to put the aggregate data on clinicaltrials.gov?

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 7:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

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Alan

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, June 07, 2013 10:19 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Thanks for the alert. As usual, we see things the same way.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On Jun 7, 2013, at 10:17 PM, "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov> wrote:

Alan,

Want to make sure you are aware that there has been some discussion at nichd about data submission from SUPPORT into ClinicalTrials.gov (aggregate, not participant level). I think (b)(5)

(b)(5)

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, June 07, 2013 9:58 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Agree.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On Jun 7, 2013, at 9:27 PM, "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov> wrote:

I am quite sure our (b)(5)

(b)(5)

NIH should probably make sure with the (b)(5)

(b)(5)

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Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Monday, June 10, 2013 6:50:57 AM

Rose and Mona,
IF Cathy hasn't seen this, please send to her. We do not physically hold the data and the data belongs to the Network. This is like any outside data request to the Network and would be guided by the Network data sharing policy and the consent forms.
Marian

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 10, 2013 6:38 AM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

From the weekend - will forward the letter
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, June 08, 2013 07:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; 'nfiner@ucsd.edu' <nfiner@ucsd.edu>
Cc: 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; 'adas@rti.org' <adas@rti.org>; Rowe, Mona (NIH/NICHD) [E]
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

I will discuss with Mona on monday.

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Saturday, June 08, 2013 05:49 AM
To: Finer, Neil <nfiner@ucsd.edu>
Cc: wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das (adas@rti.org) <adas@rti.org>; Rowe, Mona (NIH/NICHD) [E]
Subject: Re: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Since the request is not to the Federal government, I not sure that it comes under FOIA, but would ask the more legally inclined to opine. Mona can you find out and let us know what is required, if anything.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On Jun 8, 2013, at 2:55 AM, "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>> wrote:

Hello Everyone
I assume this comes under FOIA
The data is held by RTI and I would assume we would want clarity on what is being asked for
Raw data files, analyzed outcome data, downloaded oximetry data
Is there a requirement to release any and all such information?

Since that data sits with RTI, I will assume that RTI and the NIH will decide what is appropriate to release.
I will agree to whatever you believe is appropriate and responsive.
I am concerned that this data if provided in raw form can be used out of context.
How do we protect against such an occurrence?
Let me know what you plan to do
Be well
Thanks for the ongoing support
Neil

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Friday, June 07, 2013 11:16 PM
To: adas@rti.org<mailto:adas@rti.org>; wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>; Finer, Neil
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov<mailto:guttmach@mail.nih.gov>); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org<mailto:mcarome@citizen.org>
web: www.citizen.org<http://www.citizen.org/>

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing
Date: Friday, June 07, 2013 5:23:25 PM
Attachments: 130607_Letter to SUPPORT Study Investigators Requesting Study Data_FINAL_Signed.doc

---

-----Original Message-----
From: Michael Carome [mcarome@citizen.org]
Sent: Friday, June 07, 2013 05:15 PM Eastern Standard Time
To: Das, Abhik; wcarlo@peds.uab.edu; nfiner@ucsd.edu
Cc: Guttmacher, Alan (NIH/NICHD) [E] (guttmach@mail.nih.gov); Sidney Wolfe
Subject: Letter requesting SUPPORT study data in accordance with NIH policy on data sharing

Dear Drs. Das, Carlo, and Finer,

Please see the attached request for data regarding your SUPPORT study. The original hardcopy will follow by regular mail.

Thank you for your prompt attention to this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

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June 7, 2013

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
3040 East Cornwallis Road
Post Office Box 12194
Research Triangle Park, NC 27709-2194

Waldemar A. Carlo, M.D.
Director, Division of Neonatology
University of Alabama at Birmingham
Women & Infants Center
1700 6th Avenue
South Birmingham, AL 35233

Neil N. Finer, M.D.
Chief, Division of Neonatology
Department of Pediatrics
School of Medicine
University of California, San Diego
3020 Children's Way, MC 5109
San Diego, CA 92123-5109

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Drs. Das, Carlo, and Finer:

In accordance with the National Institutes of Health's (NIH's) long-standing data sharing policy,[1] which requires data sharing for all NIH-funded grants, Public Citizen's Health Research Group respectfully requests a digital copy of all individual subject-level data — without subject identifiers — obtained for the SUPPORT study that was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The data being requested includes the data on actual oxygen saturation levels that were achieved for each subject over the course of their involvement in the study. We are seeking all data for (a) the 1,316 subjects enrolled and randomly assigned to one of the four experimental groups in the SUPPORT study; and (b) those subjects who were eligible to be, but were not, enrolled in the SUPPORT study, and for whom

[1] National Institutes of Health. NIH Data Sharing Policy and Implementation Guidance. March 5, 2003. http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. Accessed June 6, 2013.

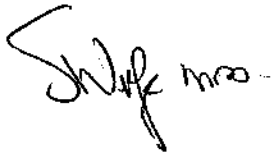
data was collected and published regarding demographics, baseline clinical characteristics, and clinical outcomes.[2]

We also respectfully request that you provide with the data (a) an explanation of the format used for storing the data; (b) a description of how the data was coded; and (c) the case report forms for each subject.

Thank you for your prompt attention to this request. Please notify us immediately if you have any questions about the data we are seeking or anticipate problems fulfilling our request.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Senior Advisor and Founder
Public Citizen's Health Research Group

cc: Dr. Allan Guttmacher, Director, National Institute of Child Health and Human Development

[2] Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics.* March 2012;129(3):480-484.

From: Wrage, Lisa Ann
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: luc.brion@utsouthwestern.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Subject: FW: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT
Date: Friday, June 07, 2013 5:04:15 PM

Hi Stephanie,
I checked the center/site combinations in this study and in this study we do have babies from UNC-CH (19-E) and U of M (5-D, I assumed this was CS Mott Children's Hospital of University of Michigan).
Thanks.
Lisa

From: Wrage, Lisa Ann
Sent: Friday, June 07, 2013 2:08 PM
To: 'Archer, Stephanie (NIH/NICHD) [E]'; luc.brion@utsouthwestern.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Subject: RE: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT

All I know is that I was to include the 11 centers that were in the NRN during 2003-2011.

I see what you are saying in terms of sub-sites changing over time. It has not been my experience in the NRN to treat sub-sites as if they are separate centers, but anyway, I've copied Abhik and Marie on this to see what they think.

Lisa

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Friday, June 07, 2013 1:54 PM
To: Wrage, Lisa Ann; luc.brion@utsouthwestern.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT

These sub-sites all started after SUPPORT was completed, I believe. So if you are excluding the main sites that were not in both cohorts, should you also exclude the sub-sites?

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, June 07, 2013 1:46 PM
To: Archer, Stephanie (NIH/NICHD) [E]; luc.brion@utsouthwestern.edu
Subject: RE: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT

The subjects are different in the before & after cohorts.
Is it enough information to know that both Duke and Wayne State were included?
Our focus was on centers not sub-sites in terms of who to include.
Lisa

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Friday, June 07, 2013 1:27 PM
To: Wrage, Lisa Ann; luc.brion@utsouthwestern.edu
Subject: RE: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT

UNC would have been with the Duke data and U of M with Wayne State. I am assuming since subjects needed to be in both birth cohorts (before and after SUPPORT) that their data was not included, correct?

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, June 07, 2013 1:11 PM
To: Archer, Stephanie (NIH/NICHD) [E]; luc.brion@utsouthwestern.edu
Subject: RE: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT

Hi Stephanie,

The centers included were:

```
/*          (b)  Case Western                          */
/*          (6)  UT Dallas (UT Southwestern)           */
/*               Wayne State                           */
/*               Emory                                 */
/*               -Cincinnati                           */
/*               -Indiana                              */
/*               -Brown                                */
/*               -Stanford                             */
/*               -Alabama                              */
/*               -Houston                              */
/*               -Duke
```

Generally I don't look at sub-sites, but it does not look like your list would be included in these centers. Let me know if this was helpful.

Thanks.

Lisa

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Friday, June 07, 2013 12:59 PM
To: Luc Brion (luc.brion@utsouthwestern.edu); Wrage, Lisa Ann
Subject: Boilerplate | LeVan, Changes in Therapy Associated with SUPPORT

Hi Lisa,

I am working on the boilerplate for Jackie LeVan's paper. Can you tell me if these sub-sites were included in this dataset?

- UNC
- U of M
- Iowa Mercy

Thanks,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Wade RIch; Frantz, Ivan; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); Petrie, Carolyn; newman@rti.org; (kzaterka@rti.org)
Subject: RE: Article of interest to SUPPORT
Date: Friday, June 07, 2013 11:22:06 AM

I find the following statement in OHRP's letter offensive to medical researchers and misinformed.

"Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation."

As clinical researchers, we also do what we think is best for our patients. We will do protocol violations whenever it is in the best interest of the patients.

Keith Barrington's blog link is enclosed. http://neonatalresearch.org/2013/06/06/well-supported/

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 07, 2013 9:45 AM
To: richard.ehrenkranz@yale.edu; nfiner@ucsd.edu; Wade RIch; Frantz, Ivan; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion

(luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); Petrie, Carolyn; newman@rti.org; (kzaterka@rti.org)
Subject: Article of interest to SUPPORT

http://www.npr.org/blogs/health/2013/06/06/189156915/nih-chief-rejects-ethics-critique-of-preemie-study

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: THANKS
Date: Thursday, June 06, 2013 8:50:46 PM

Rose.

Thank you! You are doing such a great job weathering this as well as leading the NRN.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Fri, Jun 7, 2013 00:15:34 GMT+00:00
Subject: THANKS

Wally
Thanks so much for coming to the council meeting today. It is a true pleasure to work with you.
Feedback is extremely positive and supportive.
Thanks for your hard work, dedication and perseverance!
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

Blansfield, Earl (NIH/NICHD) [E]

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, June 06, 2013 9:14 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: SUPPORT controversy, NIH website and informed consent

FYI

From: Kodish, M.D., Eric [mailto:kodishe@ccf.org]
Sent: Thursday, June 06, 2013 10:42 AM
To: Austin, Christopher (NIH/NCATS) [E]; Collins, Francis (NIH/OD) [E]
Subject: SUPPORT controversy, NIH website and informed consent

Dear Chris and Francis:

I was so pleased to see NIH take a helpful and constructive stand in yesterday's NEJM with regard to the SUPPORT study and the future of clinical trials. Surely this issue must be front and center for NCATS going forward. I was one of the signatories to the letter from leaders in bioethics and it was great to see both published in the same volume of the journal.

I wanted to bring your attention to a tool that is featured on the NIH website that may be helpful going forward. Our work on the consent process for randomized trials in children with leukemia has yielded a great deal of helpful scientific information on ways to optimize the consent process. We suspect that much of this translates into the adult context as well. The link is here: http://www.nih.gov/health/clinicaltrials/providers/tips.htm

We appreciate that this work would not have been possible without NIH support in the form of 3 consecutive RO1 grants, and are especially proud that NIH has endorsed it by putting it on its own website. As the discussion goes on and we move toward a learning health care system, there is much to be gained by redirecting attention from the consent document to the *consent process*. Please don't hesitate to let me know if I can help.

Best wishes, Rick

Eric Kodish M.D.
Center for Ethics, Humanities and Spiritual Care
FJ O'Neill Professor and Chair
Department of Bioethics
Professor of Pediatrics
Lerner College of Medicine
Cleveland Clinic

216 444-3850

http://my.clevelandclinic.org/about-cleveland-clinic/ethics-humanities-care/default.aspx

==========

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Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, June 06, 2013 4:06 PM
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Fritz, Craig (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Zuk, Dorit (NIH/NCATS) [E]; Tatem, Anne (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: ScienceInsider: U.S. Patient Protection Agency Drops Plan to Sanction Leaders of Infant Study

*Science*Insider
Breaking news and analysis from the world of science policy

U.S. Patient Protection Agency Drops Plan to Sanction Leaders of Infant Study

by David Malakoff on 6 June 2013, 1:10 PM

Breath of life. Controversial study looked at how much oxygen premature infants should receive. Credit: Wikimedia

Under fire from researchers and ethicists, the U.S. government agency responsible for protecting patients involved in scientific studies is backing away from a decision to sanction the leaders of a clinical trial involving premature infants after finding that the researchers failed to disclose the trial's full risks. "We have put on hold all compliance actions," the U.S. Office for Human Research Protections (OHRP) announced in a 4 June letter to the University of Alabama, Birmingham (UAB), which led the trial. OHRP also says that it plans to hold a public meeting to discuss the controversy, with an eye toward clarifying the rules for providing informed consent.

OHRP's move came a day before *The New England Journal of Medicine* published two pieces urging OHRP to reconsider the sanctions and expressing support for the researchers who designed and carried out the trial. "[W]e respectfully disagree with the conclusions of the OHRP," wrote three senior officials from the National Institutes of Health (NIH), which funded the study, including NIH Director Francis Collins. "Allowing the

decision to stand would be unfair to the investigators and institutions involved," wrote a group of several dozen prominent bioethicists and pediatric researchers.

The controversy came to public light in early April, after the nonprofit group Public Citizen alerted reporters to a 7 March letter from OHRP to UAB. It concluded that the 23 institutions involved in the trial, known as SUPPORT, had failed to fully disclose its risks. The letter also asked UAB to prepare a "corrective action plan." The trial, which ran from 2005 to 2009, provided 1316 extremely premature infants with different oxygen concentrations to better understand how to prevent the blindness that sometimes accompanies the treatment. The trial's results, published in 2010 in *The New England Journal of Medicine*, indicated that infants receiving lower oxygen levels were more likely to die, but less likely to become blind, than babies receiving higher levels. All of the babies received oxygen levels that were within then-accepted standards of medical care. OHRP concluded, however, that consent forms didn't adequately spell out the possible consequences, including death, of being at one end of the range or the other. And Public Citizen argued that parents would not have signed their children up for the trial if the risks had been fully explained.

The controversy sparked extensive discussion in biomedical research circles, and the trial got harsh ethical reviews in public forums such as websites. But OHRP's 4 June letter seeks to calm the waters. "OHRP has become aware of widespread misunderstanding about the risks that are required to be disclosed in obtaining informed consent for certain types of clinical trials," the letter states, adding that "we wish to emphasize that OHRP does not and has never questioned whether the design of the SUPPORT study was ethical."

But the issues involved are complex, the letter notes, and "[g]iven their importance, we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly." Not only will the agency "engage in the usual notice and comment process with regard to draft guidance," it says, "we will also conduct an open public meeting on this topic."

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Barbara Stoll"; "Wally Carlo, M.D."
Subject: RE: videocast
Date: Thursday, June 06, 2013 1:29:00 PM
Attachments: SUPPORT Council 2013-06-06 revised 6.3.2013.potx

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Thursday, June 06, 2013 1:20 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: videocast

Can you both share your slides
THANKS

BJS

NICHD
NEONATAL RESEARCH NETWORK

The SUrfactant Positive Airway Pressure and Pulse OximetRy Trial in Extremely Low Birth Weight Infants

SUPPORT Trial

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NIH National Heart, Lung, and Blood Institute

NICHD NRN Mission

The Neonatal Research Network (NRN) is designed to conduct studies to investigate the safety and efficacy of treatment and management strategies to care for newborn infants.

Origins of the NRN

Neonatal management, especially for high-risk term and preterm infants, has often adopted practices without objective evaluation

NICHD established the NRN in 1986 to address the need for well-designed clinical trials in neonatal medicine

NICHD NRN Goals

Identify priority issues for research in the promotion of infant health and prevention of disease

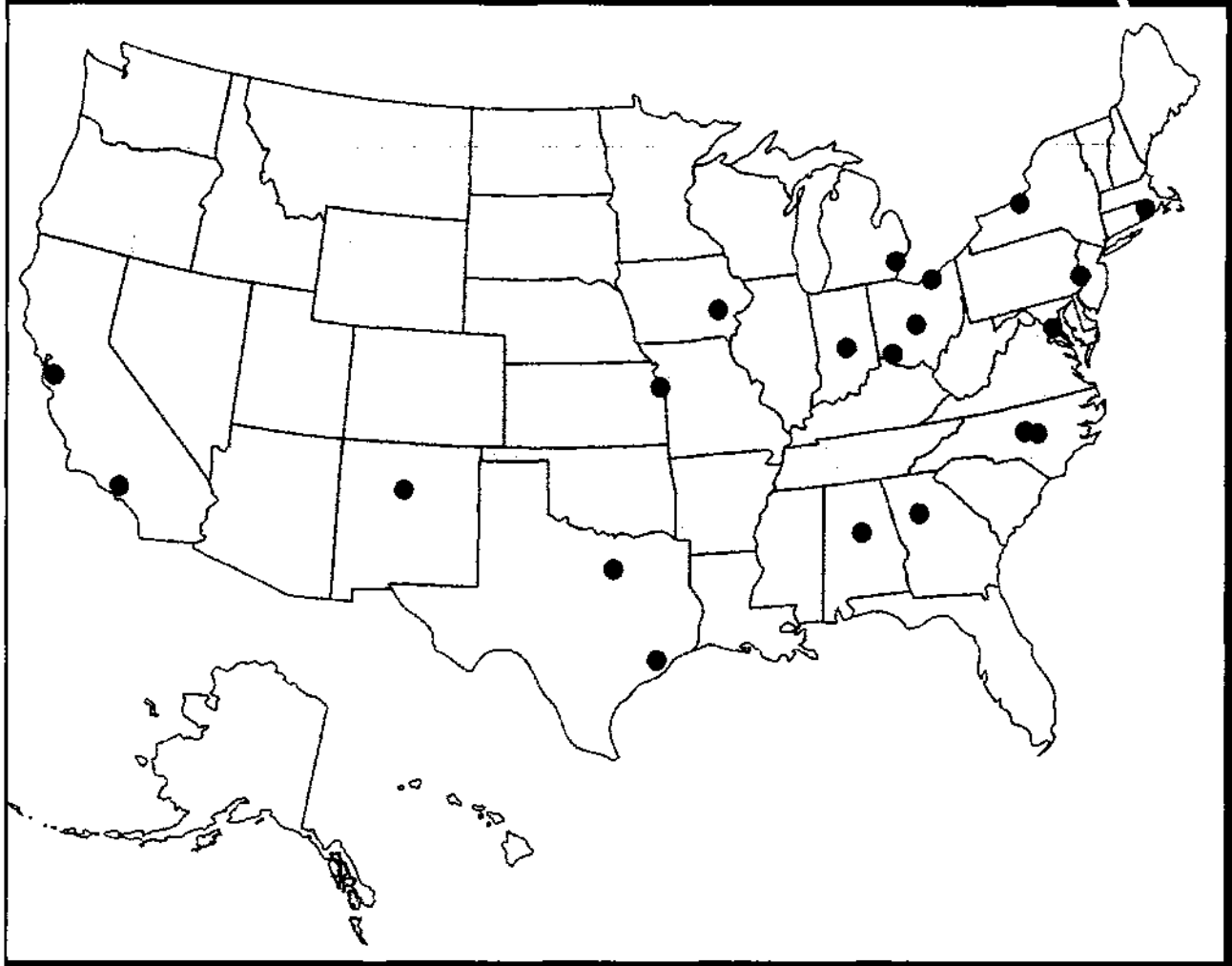
Evaluate interventions for efficacy, safety, and cost-effectiveness, including:

- Translational research
- Genetics
- New technologies

NRN Background

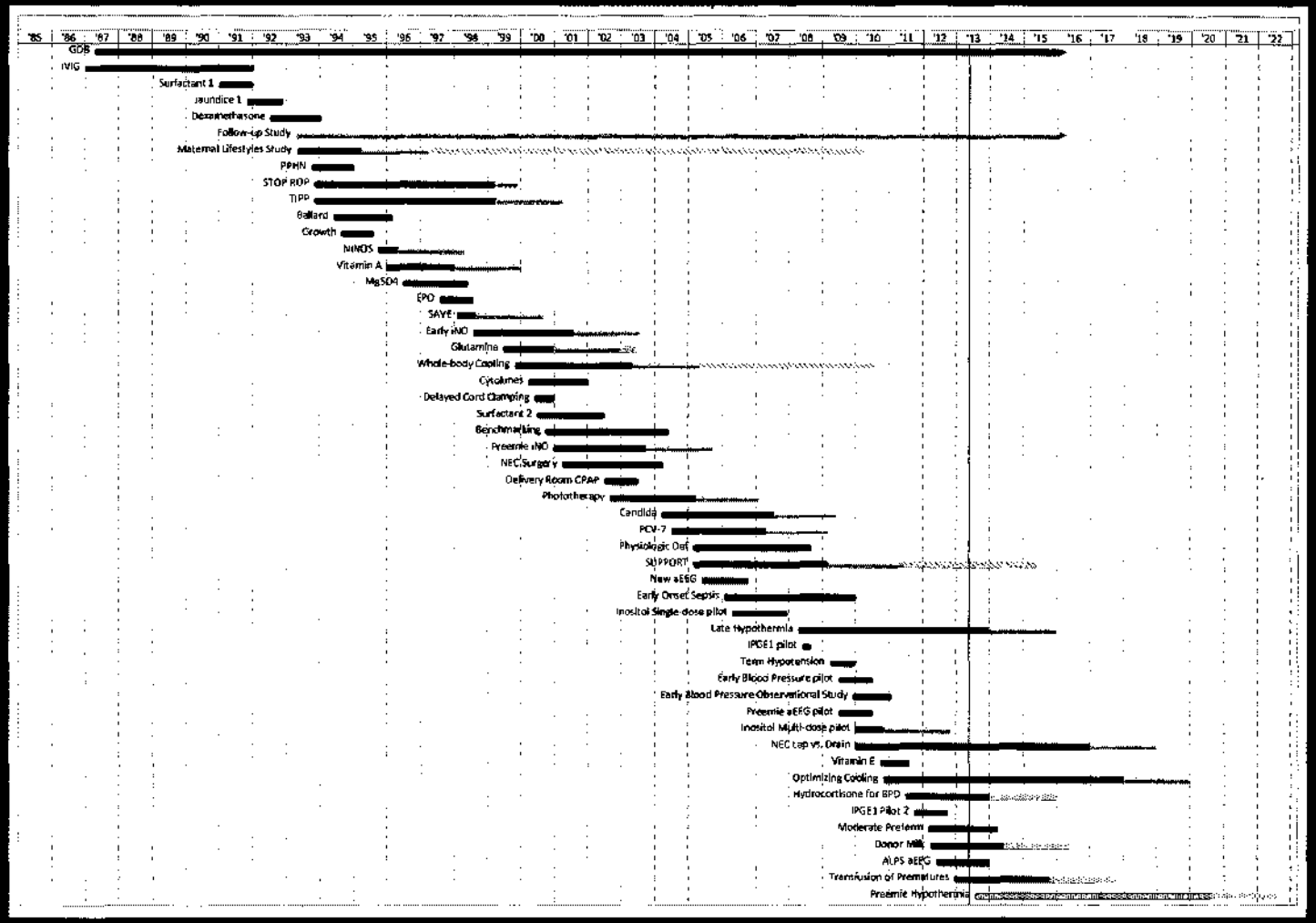
- Collaborative participation on common protocols
- Cooperative agreements
- Competitively peer-reviewed
  - Open competition
  - Content of grant, concept proposal, depth of faculty and institution
  - Priority score
  - Diversity in population

Current NRN Centers (2011-2016)



Brown University
Case Western Reserve University
Children's Mercy Hospitals and Clinics,
University of Missouri-Kansas City
Cincinnati Children's Medical Center
Duke University
Emory University
Indiana University
Nationwide Children's Hospital,
Ohio State University
RTI International
Stanford University
University of Alabama at Birmingham
University of California – Los Angeles
University of Iowa
University of New Mexico
University of Pennsylvania
University of Rochester
University of Texas Southwestern
University of Texas Health Science Center
Wayne State University

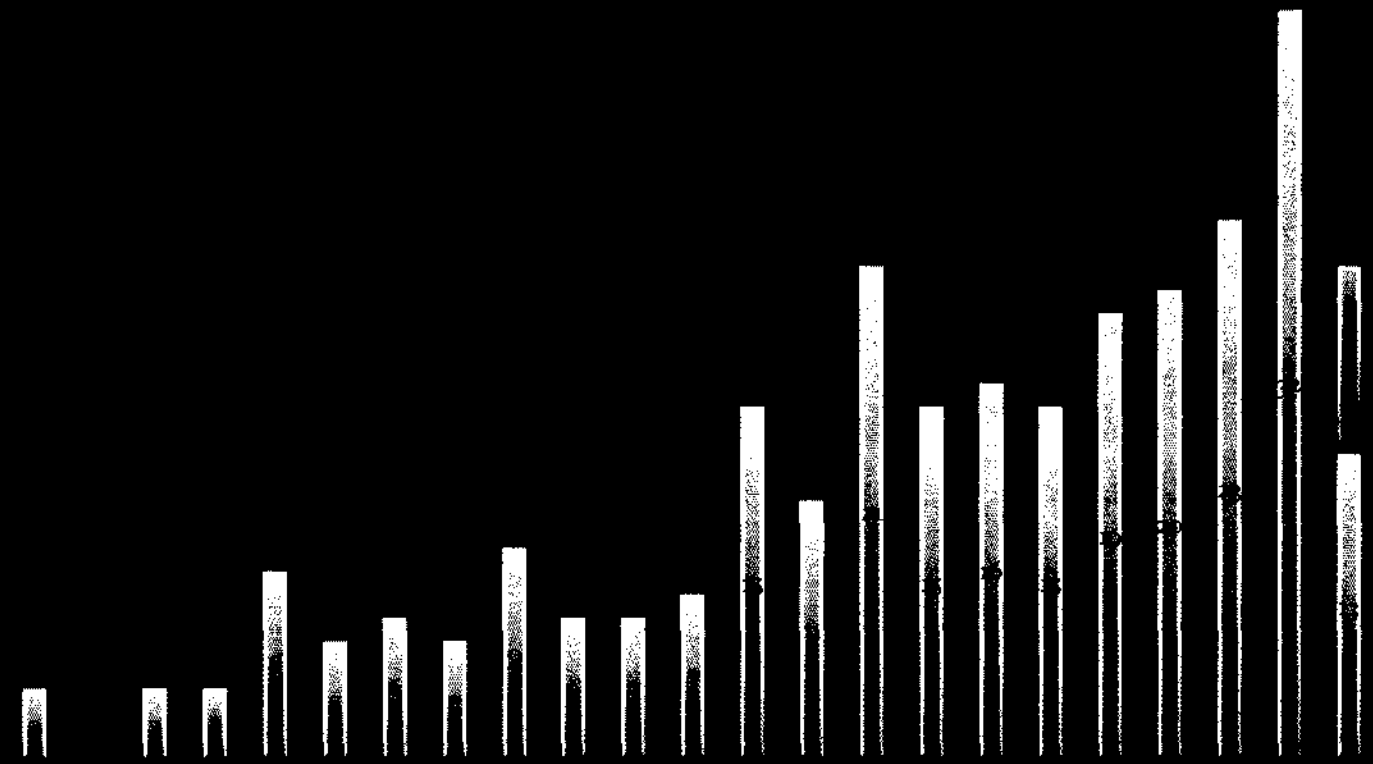
NRN Protocols



NEONATAL RESEARCH NETWORK

NRN Publications

NEJM – 17 papers
JAMA – 4 papers



DENTAL RESEARCH NETWORK

NRN Contributions to Patient Care

Topic	Impact on Clinical Practice	NICHD research continuing to the impact on clinical practice
Perinatal care at the threshold of Viability	AAP Clinical report, 2002 Pediatrics 2002;110:1024-27	NRN citations Lemons JA et al, Pediatrics 2000;107:1 Vohr BR et al, Pediatrics 2000;105:1216-26
Surfactant administration	AAP Clinical Report 2008 Pediatrics 2008;121:419-432	Vohr BR et al, Pediatrics 2000;105:1216-26 Wright LL et al Am J Obstet Gynecol 1992;166:646-651 Finer NN et al, Pediatrics 2004;114:651-657
Infection and neurodevelopmental impairment	CDC prevention of GSB treatment guidelines; 2010 increased vigilance for pathogens and follow-up for ELBW infants	NRN Network, Stoll et al , JAMA 2004 Stoll et al, NEJM 2002; 347:240-247 Stoll Et al, Ped Infect Dis J. 2005
Periviable web based outcomes tool	Source of information for threatened preterm birth at 22-25 weeks gestation; Link is on AAP NRP website	NRN Network, Tyson et al, NEJM 2008

NEONATAL RESEARCH NETWORK

NRN Contributions to Patient Care

Topic	Impact on Clinical Practice	NICHD research continuing to the impact on clinical practice
Levels of neonatal care	AAP Policy Statement: Classification and organization of neonatal facilities to care for NICU patients, Pediatrics 2004;114:1341-47	Lemons JA et al, Pediatrics 2000;107:1
Follow up of high risk infants	AAP Policy Statement: Hospital discharge of the high-risk neonate, Pediatrics 2008;122:1119-1126	Vohr et al, Pediatrics 2004;114 (5 suppl):1377-1397 Vohr BR et al, Semin Perinatol 2003;27:333-342
Post natal Steroids	AAP Policy Statement: Postnatal Corticosteroids to prevent or treat BPD, Pediatrics 2010;126:800-808	Walsh MC et al, Pediatrics 2007;119:876-890 Vohr BR et al, Pediatrics 2005;116:635-643 Walsh MC et al, Pediatrics 2006; epages 118/5/e1328 Wilson-Costello D et al, Pediatrics 2009 epages 123/3/e430
Antenatal corticosteroids	ACOG Committee Opinion Number 475: Antenatal Corticosteroid Therapy for Fetal Maturations. Obstetrics and Gynecology 2011;117:422-424.	Lee BH et. al, Pediatrics 2008;121:289-96.
Breast Feeding	AAP Policy Statement on Breast feeding 2013	Vohr BR Pediatrics 2006, Vohr BR Pediatrics 2007, Meinzen-Derr J Perinatology 2009, Hintz SR Pediatrics 2005

NRN Contributions to Patient Care
Randomized trials – Seminal Contributions

- Inhaled nitric oxide for persistent pulmonary hypertension –studies led to FDA drug approval (*NEJM 1997;336:597-604)*
- Vitamin A for prevention of BPD (*NEJM* 1999; 340:1962-1968)
- Whole body cooling for encephalopathy (*NEJM* 2005; 353:1574-1584 and *NEJM* 2012; 366:2085-2092)

Important Questions: SUPPORT Study

- How best to assist breathing after delivery of extremely premature infant?
  - Surfactant – best studied neonatal drug – need endotracheal tube in place
  - Surfactant studies pre-dated widespread use of antenatal corticosteroids
  - Continuous Positive Airway Pressure works in some infants
- Where to target oxygen saturation?
  - Higher levels – higher retinopathy and lung disease

NEONATAL RESEARCH NETWORK

Neonatal Practice 2003-2004

Trend towards more use of CPAP – some infants were capable of sustaining their own ventilation without intubation

Trend towards use of lower oxygen saturation targets – published reports of saturations in the 80's with lower ROP and no mortality effect

State of the Science 2003-2004

24-27 week infants oxygen target saturations 85-95%
Research was testing standard care practice

Overall level of oxygen target saturation was not changed; it was targeted in two ranges within standard of practice

No data to suggest an increase in mortality at the outset of the study

SUPPORT Research Questions

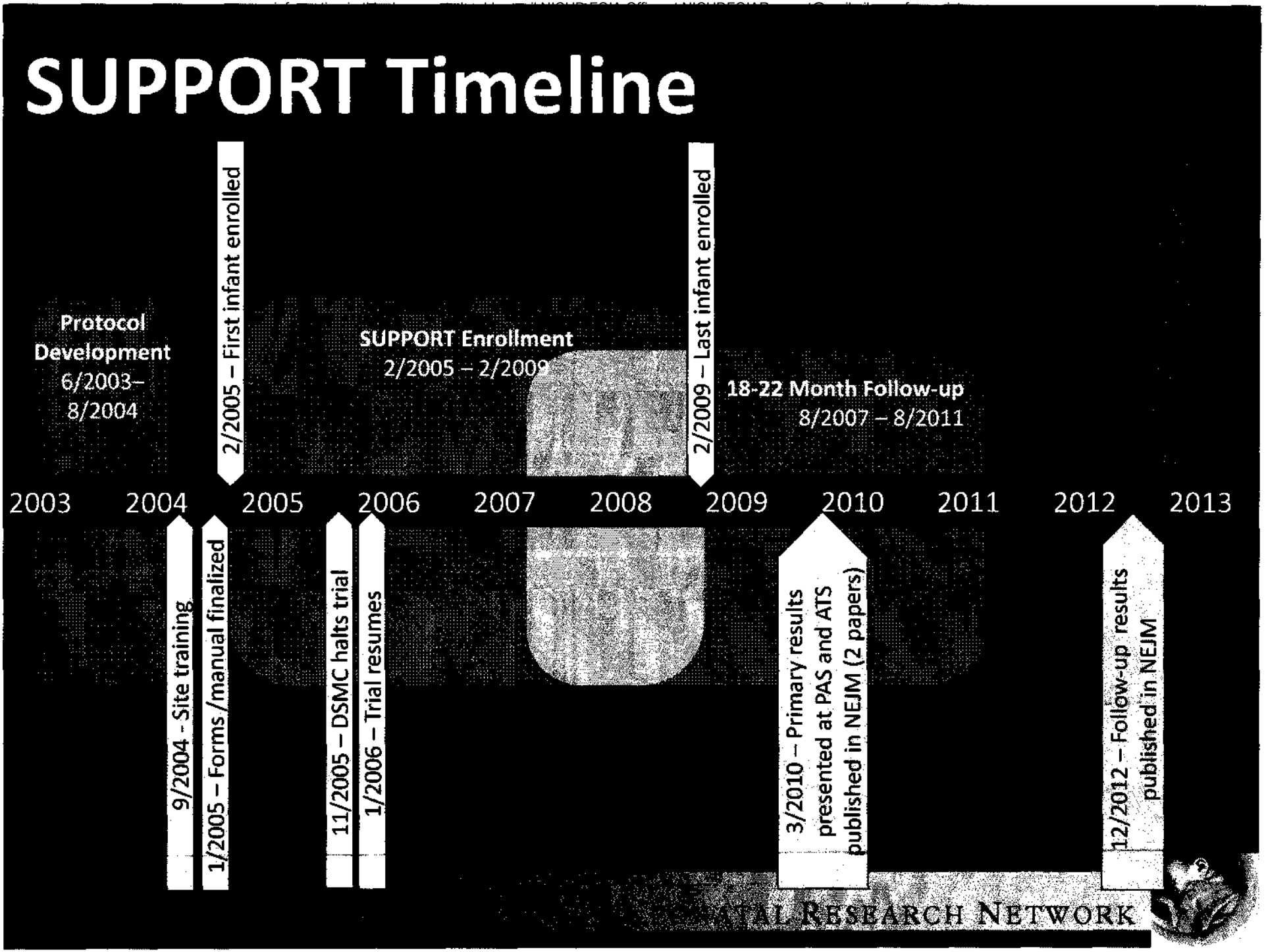
Where do we target saturations for optimal outcome?

- Low 90's
- Mid-high 80's

What's better?

- Early Surfactant
- CPAP

NEONATAL RESEARCH NETWORK



Study Results

In-hospital

Follow up at 18 -22 months

To be presented by:

Dr. Wally Carlo

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

NATAL RESEARCH NETWORK

NICHD Neonatal Research Network SUPPORT Trial Centers (2004-2009)

Brown University
Case Western Reserve University
Duke University
Emory University
Indiana University
Research Triangle Institute
Stanford University
Tufts Medical Center
University of Alabama – Birmingham
University of Cincinnati
University of California – San Diego
University of Iowa
University of Miami
University of New Mexico
University of Rochester
University of Texas, Southwestern – Dallas
University of Texas – Houston
University of Utah
Wayne State University
Wake Forest University
Yale University

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NEONATAL RESEARCH NETWORK

Blansfield, Earl (NIH/NICHD) [E]

From: Shurin, Susan (NIH/NHLBI) [E]
Sent: Thursday, June 06, 2013 12:24 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: OHRP

Hi, Alan and Kathy,

(b)(5) : "Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and researchers," the OHRP's Lisa Buchanan writes. "Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation."

(b)(5)

We should (b)(5) it's picked up by NPR, http://www.npr.org/blogs/health/2013/06/06/189156915/nih-chief-rejects-ethics-critique-of-preemie-study.

Susan

Susan B. Shurin, MD, Deputy Director
National Heart, Lung, and Blood Institute (NHLBI)
31 Center Drive, 5A48
Bethesda MD 20892
301-496-1078
shurinsb@nhlbi.nih.gov

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Scan of the WSJ article
Date: Thursday, June 06, 2013 12:20:42 PM
Attachments: WSJ_SUPPORT_2013-0606.pdf

From today's Wall Street Journal.

Thanks

Abhik

Blansfield, Earl (NIH/NICHD) [E]

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, June 06, 2013 11:06 AM
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Fritz, Craig (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Zuk, Dorit (NIH/NCATS) [E]; Tatem, Anne (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: NYT and NPR Stories on OHRP Action/NEJM Letter

New York Times

June 5, 2013

Watchdog Halts Action on Researchers

By JAN HOFFMAN

The federal Office for Human Research Protections announced on Wednesday that it would suspend action against the University of Alabama at Birmingham, which it said in March did not adequately inform parents about the risks to their premature infants of enrollment in a large research trial.

In a letter dated Tuesday, the watchdog office still maintained that researchers had not properly informed parents, and that it could still require that the university and 22 other trial sites, which include many of the country's top research universities, take corrective action. But it also acknowledged that federal guidelines about a researcher's obligations needed to be clarified and issued. On the office's Web site, the federal Department of Health and Human Services announced that a public meeting to debate such guidelines was forthcoming.

The timing of the letter coincided with the publication on the Web site of The New England Journal of Medicine of an opinion article by leaders of the National Institutes of Health that took issue with the agency's initial condemnation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial, widely known as Support. Both the agency and the N.I.H. are branches of Health and Human Services.

The Journal also published a letter, signed by 46 doctors and scholars, that criticized the office's initial action as overreaching and having a potentially chilling effect on essential research.

At the center of the uproar, which has engendered commentary from scientists, is whether researchers needed to disclose to parents the risks of a randomized trial of higher and lower oxygen levels administered to premature infants. The levels of oxygen concentration given to the infants were within the range of 85 percent to 95 percent, the standard treatment recommended by the American Academy of Pediatrics. Researchers wanted to pinpoint more precisely the level at which the risks of eye damage or neurological damage, or even death, were abated.

There were risks to the infants at either end of the narrow band. The results, published in The New England Journal of Medicine in 2010, showed that lowering the oxygen levels led to greater mortality rates than expected.

But as the office wrote, "Some physicians, recognizing the particular concerns about risks near the low (85 percent) and high (95 percent) ends of that range, might choose to avoid one or both of those regions."

Dr. Joel E. Frader, a pediatrician and professor of medical humanities and bioethics at Northwestern, who signed the letter in The Journal, felt that the office initially did overreach, but also that the researchers did not properly inform parents of all risks. Because there was a band of oxygen saturation levels, he said, there was no clear standard of care for these infants, only an "acceptable range." And parents should have been told that, he said.

"It's the obligation of investigators to say, 'Here's the debate, here's how we're trying to answer the question, and that involves the possibility that there is an additional risk with being a research subject,' " he said.

He applauded the effort to clarify guidelines for disclosure, even in standard-of-care trials. Researchers should not shy away from fully informing subjects, he said. "There is no empirical evidence that transparency and clarity decreases participation in clinical research," he said.

NPR

Policy-ish

NIH Chief Rejects Ethics Critique Of Preemie Study

by Richard Knox
June 06, 2013 8:58 AM

National Institutes of Health Director Dr. Francis Collins contested criticism that researchers running a study of premature infants didn't adequately advise parents about the risks.

Charles Dharapak/AP

The chief of the National Institutes of Health is disavowing a ruling from the government office that oversees the ethics of human research.

At issue is a controversial study of more than 1,300 severely premature infants. This spring, the federal Office for Human Research Protections criticized the scientists who ran the study for failing to tell parents about the risks their newborn children might face.

"We respectfully disagree," NIH director Dr. Francis Collins and two colleagues say, in an unusual public disagreement within the government over research ethics.

At the same time, the Office for Human Research Protections or OHRP told the University of Alabama at Birmingham, one of the study sites, that it was suspending disciplinary action on the matter until ethics guidelines on such studies are clarified.

The watchdog office also says it won't proceed against sponsors of similar studies for now. But it held open the possibility that the Alabama medical center and 22 other trial sites could still face sanctions. The OHRP is an arm of the Department of Health and Human Services, the NIH's parent agency.

In a commentary published by the *New England Journal of Medicine*, Collins and company write that "this controversy has alarmed some of the parents of infants who were in the study, confused the biomedical research community, and befuddled IRBs," the Institutional Review Boards that oversee human research at every clinical center.

Collins' coauthors are Kathy Hudson, NIH's deputy director for science, outreach and policy, and Dr. Alan Guttmacher, director of the National Institute of Child Health and Human Development.

The three say they have "a fundamental difference in interpretations" over what doctors knew about how to treat preemies at the time the multicenter study was launched, back in 2004.

The government's research watchdogs say the study's authors should have warned patients that children receiving lower doses of oxygen might be at higher risk of nerve damage and death.

But Collins and other defenders of the study, called SUPPORT, say data available back in 2004 gave "no reason to foresee that infants in one study group would have a higher risk of death that would those in the other group."

The commentary is accompanied by a letter roundly supporting the disputed study that is signed by 46 ethicists and pediatricians.

The ruling of the OHRP is "unfair to the investigators and institutions involved in SUPPORT," the letter says. Allowing it to stand "would...set a precedent that would impede ongoing and future...outcomes studies."

While the letter's signatories say the OHRP "overreaches" in concluding that the study violated federal ethics guidelines, they "acknowledge that the permission forms could have been improved" and "the consent process for clinical research can no doubt be improved."

They did not specify how the SUPPORT study's consent process fell short.

Collins and his colleagues also say the controversy serves as an occasion for "a substantive national dialogue" about "how best to respect and protect participants in research studies conducted within the standard of care and how to define 'reasonably foreseeable risks' in this setting."

The phrase "standard of care" is at the heart of the matter. Basically, the NIH leaders say the SUPPORT controversy raises issues that apply to any research that aims to test and improve accepted medical practice.

Thus, the case could turn out to have far-reaching effects on future clinical research.

To underscore that, HHS announced Wednesday that it plans to hold a public meeting to discuss how federal regulations designed to protect human research subjects should be applied to studies that probe "standard of care treatment."

The upcoming meeting, whose date has not been set, will address how Institutional Review Boards should assess the risks of studies looking at current clinical practice and what "reasonably foreseeable risks" should be disclosed to study volunteers.

OHRP's six-page letter sent Tuesday to Alabama researchers suggests how complicated and subtle an issue this is.

The letter acknowledges that some doctors treating a premature infant might avoid giving oxygen at levels at either end of the range used in the SUPPORT study. But by enrolling their infants in the study, parents were waiving their children's right to such individualized treatment.

"Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and researchers," the OHRP's Lisa Buchanan writes. "Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation."

As a "crucial trade-off" in doing clinical research, Buchanan writes, "society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed."

Another effect of the controversy: HHS plans to set up a process for researchers and institutions to appeal the rulings of the Office of Human Research Protections "in those situations in which reasonable people disagree about the actions taken."

Currently, there is no appeal from the Office's rulings. Dr. Michael Carome of Public Citizen, an advocacy group that first complained about the SUPPORT study, says the OHRP letter is "an important step toward addressing a highly unethical trial."

But Carome said HHS's decision to allow "current similar trials to continue ... is an abject and unacceptable failure to protect human subjects in clinical trials."

From: Shankaran, Seetha
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo
Subject: RE: Neonatal Case O-002671
Date: Thursday, June 06, 2013 11:10:35 AM

Thanks Neil
Yes, the support for SUPPORT has been overwhelming--thanks Rose
I am waiting to see what the WSU situation is
Seetha

From: Finer, Neil [nfiner@ucsd.edu]
Sent: Thursday, June 06, 2013 10:19 AM
To: Shankaran, Seetha; Rose; Wally Carlo
Subject: RE: Neonatal Case O-002671

Hi Seetha Rose and Wally
I saw and thanked Henry
Amazing what these people will do –Perhaps we ought to sign up as experts – That would end the suits before they started
Be well
Neil

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Thursday, June 06, 2013 3:58 PM
To: Rose; Wally Carlo; Finer, Neil
Subject: Fwd: Neonatal Case O-002671

Rose
FYI--I am sure Wally and Neil have seen this
Seetha

Sent from my iPhone

Begin forwarded message:

From: Henry Rozycki <hrozycki@mcvh-vcu.edu>
Date: June 6, 2013 8:40:52 AM EDT
To: "DIRNBERGER, DANIEL R LtCol USAF AETC 59 MCCS/SGOBP" <daniel.dirnberger@us.af.mil>, Janell Fuller <JaFuller@salud.unm.edu>, "david.sheftel-md@advocatehealth.com" <david.sheftel-md@advocatehealth.com>, "welty@bcm.edu" <welty@bcm.edu>, "dpursley@bidmc.harvard.edu" <dpursley@bidmc.harvard.edu>, "slakshmi@buffalo.edu" <slakshmi@buffalo.edu>, "james.greenberg@cchmc.org" <james.greenberg@cchmc.org>, "jeff.whitsett@cchmc.org" <jeff.whitsett@cchmc.org>, "vherson@ccmckids.org" <vherson@ccmckids.org>, "bshort@childrensnational.org" <bshort@childrensnational.org>, "doelberg@chkd.com" <doelberg@chkd.com>, "ISeri@chla.usc.edu" <ISeri@chla.usc.edu>, "hkilbride@cmh.edu" <hkilbride@cmh.edu>, "rap32@columbia.edu" <rap32@columbia.edu>, "charles.simmons@cshs.org" <charles.simmons@cshs.org>, "william.h.edwards@dartmouth.edu" <william.h.edwards@dartmouth.edu>, "jaranda@downstate.edu"

<jaranda@downstate.edu>, "maria.delivoria-papdopoulos@drexelmed.edu" <maria.delivoria-papdopoulos@drexelmed.edu>, "cummingsj@ecu.edu" <cummingsj@ecu.edu>, "poratr@einstein.edu" <poratr@einstein.edu>, "dennery@email.chop.edu" <dennery@email.chop.edu>, "dpcarlt@emory.edu" <dpcarlt@emory.edu>, "jatindeb@georgiahealth.edu" <jatindeb@georgiahealth.edu>, "subramas@gunet.georgetown.edu" <subramas@gunet.georgetown.edu>, "pardalosj@health.missouri.edu" <pardalosj@health.missouri.edu>, "lrubin@health.usf.edu" <lrubin@health.usf.edu>, "sumapyati@hotmail.com" <sumapyati@hotmail.com>, "robert.lane@hsc.utah.edu" <robert.lane@hsc.utah.edu>, "dingram@iupui.edu" <dingram@iupui.edu>, "elawson@jhmi.edu" <elawson@jhmi.edu>, "cneal@kapiolani.org" <cneal@kapiolani.org>, "cole@kids.wustl.edu" <cole@kids.wustl.edu>, "vrehan@labiomed.org" <vrehan@labiomed.org>, "davidson@lij.edu" <davidson@lij.edu>, "ddeming@llu.edu" <ddeming@llu.edu>, "david.adamkin@louisville.edu" <david.adamkin@louisville.edu>, "bbarke@lsuhsc.edu" <bbarke@lsuhsc.edu>, "horganm@mail.amc.edu" <horganm@mail.amc.edu>, "ddurand@mail.cho.org" <ddurand@mail.cho.org>, "gsilverman@mail.magee.edu" <gsilverman@mail.magee.edu>, "dmcava@mail.med.cornell.edu" <dmcava@mail.med.cornell.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, Henry Rozycki <hrozycki@mcvh-vcu.edu>, Karen Hendricks-Munoz <khendricks-munoz@mcvh-vcu.edu>, "gkonduri@mcw.edu" <gkonduri@mcw.edu>, "jmp2007@med.cornell.edu" <jmp2007@med.cornell.edu>, "jbarks@med.umich.edu" <jbarks@med.umich.edu>, "wayne_price@med.unc.edu" <wayne_price@med.unc.edu>, "sshankar@med.wayne.edu" <sshankar@med.wayne.edu>, "udevaskar@mednet.ucla.edu" <udevaskar@mednet.ucla.edu>, "jmoore@metrohealth.org" <jmoore@metrohealth.org>, "ebancalari@miami.edu" <ebancalari@miami.edu>, "dcampbel@montefiore.org" <dcampbel@montefiore.org>, "ian.holzman@mssm.edu" <ian.holzman@mssm.edu>, "gewolb@msu.edu" <gewolb@msu.edu>, "annibald@musc.edu" <annibald@musc.edu>, "leif.nelin@nationwidechildrens.org" <leif.nelin@nationwidechildrens.org>, "jlarson@nemours.org" <jlarson@nemours.org>, "r-steinhorn@northwestern.edu" <r-steinhorn@northwestern.edu>, "shsridhar@notes.cc.sunysb.edu" <shsridhar@notes.cc.sunysb.edu>, "edmund_lagamma@nymc.edu" <edmund_lagamma@nymc.edu>, "pradeep.mally@nyumc.org" <pradeep.mally@nyumc.org>, "schelonk@ohsu.edu" <schelonk@ohsu.edu>, "marilyn-escobedo@ouhsc.edu" <marilyn-escobedo@ouhsc.edu>, "sringer@partners.org" <sringer@partners.org>, "pillersd@pediatrics.wisc.edu" <pillersd@pediatrics.wisc.edu>, "abedrick@peds.arizona.edu" <abedrick@peds.arizona.edu>, "wcarlo@peds.uab.edu" <wcarlo@peds.uab.edu>, "rowitchd@peds.ucsf.edu" <rowitchd@peds.ucsf.edu>, "burchdj@peds.ufl.edu" <burchdj@peds.ufl.edu>, "cbearer@peds.umaryland.edu" <cbearer@peds.umaryland.edu>, "mivalcar@prtc.net" <mivalcar@prtc.net>, "cpalmer@psu.edu" <cpalmer@psu.edu>, "keenanwj@slu.edu" <keenanwj@slu.edu>, "benitzwe@stanford.edu" <benitzwe@stanford.edu>,

"stella.kourembanas@tch.harvard.edu" <stella.kourembanas@tch.harvard.edu>, "wilkening.randall@tchden.org" <wilkening.randall@tchden.org>, "sewelty@texaschildrens.org" <sewelty@texaschildrens.org>, "jdavis@tuftsmedicalcenter.org" <jdavis@tuftsmedicalcenter.org>, "pgordon1@tulane.edu" <pgordon1@tulane.edu>, "cgleason@u.washington.edu" <cgleason@u.washington.edu>, "arringtonRobertW@uams.edu" <arringtonRobertW@uams.edu>, "jmmilstein@ucdavis.edu" <jmmilstein@ucdavis.edu>, "klee@uchicago.edu" <klee@uchicago.edu>, "wlm1@uchicago.edu" <wlm1@uchicago.edu>, "ccuy@uci.edu" <ccuy@uci.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "michele.walsh@uhhospitals.org" <michele.walsh@uhhospitals.org>, "akhil1@uic.edu" <akhil1@uic.edu>, "jeffrey-segar@uiowa.edu" <jeffrey-segar@uiowa.edu>, "hbada2@uky.edu" <hbada2@uky.edu>, "weinbebi@umdnj.edu" <weinbebi@umdnj.edu>, "bednaref@ummhc.org" <bednaref@ummhc.org>, "georg001@umn.edu" <georg001@umn.edu>, "william_maniscalco@urmc.rochester.edu" <william_maniscalco@urmc.rochester.edu>, "eric.c.eichenwald@uth.tmc.edu" <eric.c.eichenwald@uth.tmc.edu>, "rdhanire@uthsc.edu" <rdhanire@uthsc.edu>, "seidner@uthscsa.edu" <seidner@uthscsa.edu>, "jrich@utmb.edu" <jrich@utmb.edu>, "rashmin.savani@utsouthwestern.edu" <rashmin.savani@utsouthwestern.edu>, "ras9q@virginia.edu" <ras9q@virginia.edu>, "roger.soll@vtmednet.org" <roger.soll@vtmednet.org>, "Mario A. Rojas" <mrojas@wakehealth.edu>, "jpadbury@wihri.org" <jpadbury@wihri.org>, "nhanna@winthrop.org" <nhanna@winthrop.org>, "ian.gross@yale.edu" <ian.gross@yale.edu>

Subject: Fw: Neonatal Case O-002671

I received this earlier this week and thought the community might like to know what some members of the legal community are doing (no surprise). My response was that I would be happy to review and testify to the fact that the SUPPORT trial was conducted to the highest ethical standards with the best knowledge available at the time and that the subjects were fortunate to have enrolled. I have not heard back from them.

If real experts cannot be found to testify to the false theory of causation and false breach of standard theory these people are propounding, there will be no case.

Henry J. Rozycki, M.D.
Division of Neonatal-Perinatal Medicine
Medical Director, Pediatric Research Office
Associate Professor of Pediatrics
Children's Hospital of Richmond at VCU
P.O Box 980276
Richmond, VA 23298-0276
Ph: 804-828-9964
Fax: 804-828-6662
email: hrozycki@mcvh-vcu.edu

-----Forwarded by Henry Rozycki/Notes/MCVH on 06/06/2013 08:37AM -----
To: <hrozycki@mcvh-vcu.edu>
From: LCMT <lcmt@theexpertinstitute.com>

Date: 06/04/2013 03:50PM
Subject: Neonatal Case O-002671

Dr. Rozycki,

I hope you are having a great day. We have a new case that we need reviewed by an experienced neonatologist. Case details are below.

This case involves a class action suit taken up by the Federal Office for Human Research Protections which concluded that consent forms, used in a study of optimal oxygen saturation in premature infants, failed to reveal that there was a greater risk of dying in the low-oxygen group and a greater risk of severe eye damage in the high oxygen group. The consent form explicitly stated that, both groups would receive oxygen within the standard of care, and that there would be no predictable increase in risk no matter which randomized group the infant was in. The federal agency also found that many infants may have faced greater risks by participating, specifically, if a baby whose clinical needs might ordinarily have led doctors to deliver a relatively high level of oxygen was enrolled in the study, the infant might be randomly assigned to receive lower levels of oxygen. Additionally, the consent forms failed to sufficiently explain the potential risks of retinopathy of prematurity or death with using the experimental lower or higher oxygen saturation targets. All participating centers of this study had similar problems with their consent forms and the failure to disclose such critically important information directly affected parents' decisions to enroll their premature infants in this study.

An expert in Neonatology is needed to evaluate what individualized treatment of each premature infant would have looked like. For example, are there clinical signs or symptoms that are monitored during the course of treatment which would lead the treating doctor to decide whether to raise or lower the oxygen, or maintain the same level, on an ongoing basis? If that is the case, what research exists to show that such individualized care and treatment improves the outcomes?

If this is a case that you would be interested in reviewing, please provide me with your CV and fee schedule along with your answers to the questions above. Also, please let me know your litigation history (approximately how many cases you review per year, number of times being deposed, number of times at trial, percentage split between plaintiff and defense work).

If you have any questions about this case or how we work, please do not hesitate to give me a call on my direct line at 646.216.2338.

Best,

Zachary Barreto

VP of Litigation Support Services

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Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, June 06, 2013 10:41 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]
Cc: Rush, Katie (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUPPORT On NPR site too

Wonder what the connection to NPR could be- -but in case you didn't see

http://www.npr.org/blogs/health/2013/06/06/189156915/nih-chief-rejects-ethics-critique-of-preemie-study

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

-----Original Message-----
From: Stile, Christina (NIH/NICHD) [E]
Sent: Thursday, June 06, 2013 10:38 AM
To: Artis, Shavon (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Fowler-Lee, Triesta (NIH/NICHD) [E]; Machalek, Alisa Zapp (NIH/NIGMS) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Stein, Dayle (NIH/NICHD) [C]; Tillman, June (NIH/NICHD) [E]
Cc: Stile, Christina (NIH/NICHD) [E]
Subject: FYI

http://www.npr.org/blogs/health/2013/06/06/189156915/nih-chief-rejects-ethics-critique-of-preemie-study

christina stile, ELS
public information and communications branch eunice kennedy shriver national institute of child health and human development (NICHD)

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: Neonatal Case O-002671
Date: Thursday, June 06, 2013 10:22:49 AM

Wally

-----Original message-----

From: Henry Rozycki <hrozycki@mcvh-vcu.edu>
To: "DIRNBERGER, DANIEL R LtCol USAF AETC 59 MCCS/SGOBP" <daniel.dirnberger@us.af.mil>, Janell Fuller <JaFuller@salud.unm.edu>, "david.sheftel-md@advocatehealth.com" <david.sheftel-md@advocatehealth.com>, "welty@bcm.edu" <welty@bcm.edu>, "dpursley@bidmc.harvard.edu" <dpursley@bidmc.harvard.edu>, "slakshmi@buffalo.edu" <slakshmi@buffalo.edu>, "james.greenberg@cchmc.org" <james.greenberg@cchmc.org>, "jeff.whitsett@cchmc.org" <jeff.whitsett@cchmc.org>, "vherson@ccmckids.org" <vherson@ccmckids.org>, "bshort@childrensnational.org" <bshort@childrensnational.org>, "doelberg@chkd.com" <doelberg@chkd.com>, "ISeri@chla.usc.edu" <ISeri@chla.usc.edu>, "hkilbride@cmh.edu" <hkilbride@cmh.edu>, "rap32@columbia.edu" <rap32@columbia.edu>, "charles.simmons@cshs.org" <charles.simmons@cshs.org>, "william.h.edwards@dartmouth.edu" <william.h.edwards@dartmouth.edu>, "jaranda@downstate.edu" <jaranda@downstate.edu>, "maria.delivoria-papdopoulos@drexelmed.edu" <maria.delivoria-papdopoulos@drexelmed.edu>, "cummingsj@ecu.edu" <cummingsj@ecu.edu>, "poratr@einstein.edu" <poratr@einstein.edu>, "dennery@email.chop.edu" <dennery@email.chop.edu>, "dpcarlt@emory.edu" <dpcarlt@emory.edu>, "jatindeb@georgiahealth.edu" <jatindeb@georgiahealth.edu>, "subramas@gunet.georgetown.edu" <subramas@gunet.georgetown.edu>, "pardalosj@health.missouri.edu" <pardalosj@health.missouri.edu>, "lrubin@health.usf.edu" <lrubin@health.usf.edu>, (b)(6) @hotmail.com" (b)(6) @hotmail.com>, "robert.lane@hsc.utah.edu" <robert.lane@hsc.utah.edu>, "dingram@iupui.edu" <dingram@iupui.edu>, "elawson@jhmi.edu" <elawson@jhmi.edu>, "cneal@kapiolani.org" <cneal@kapiolani.org>, "cole@kids.wustl.edu" <cole@kids.wustl.edu>, "vrehan@labiomed.org" <vrehan@labiomed.org>, "davidson@lij.edu" <davidson@lij.edu>, "ddeming@llu.edu" <ddeming@llu.edu>, "david.adamkin@louisville.edu" <david.adamkin@louisville.edu>, "bbarke@lsuhsc.edu" <bbarke@lsuhsc.edu>, "horganm@mail.amc.edu" <horganm@mail.amc.edu>, "ddurand@mail.cho.org" <ddurand@mail.cho.org>, "gsilverman@mail.magee.edu" <gsilverman@mail.magee.edu>, "dmcava@mail.med.cornell.edu" <dmcava@mail.med.cornell.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, Henry Rozycki <hrozycki@mcvh-vcu.edu>, Karen Hendricks-Munoz <khendricks-munoz@mcvh-vcu.edu>, "gkonduri@mcw.edu" <gkonduri@mcw.edu>, "jmp2007@med.cornell.edu" <jmp2007@med.cornell.edu>, "jbarks@med.umich.edu" <jbarks@med.umich.edu>, "wayne_price@med.unc.edu" <wayne_price@med.unc.edu>, "sshankar@med.wayne.edu" <sshankar@med.wayne.edu>, "udevaskar@mednet.ucla.edu" <udevaskar@mednet.ucla.edu>, "jmoore@metrohealth.org" <jmoore@metrohealth.org>, "ebancalari@miami.edu" <ebancalari@miami.edu>, "dcampbel@montefiore.org" <dcampbel@montefiore.org>, "ian.holzman@mssm.edu" <ian.holzman@mssm.edu>,

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Sent: Thu, Jun 6, 2013 12:40:52 GMT+00:00
Subject: Fw: Neonatal Case O-002671

I received this earlier this week and thought the community might like to know what some members of the legal community are doing (no surprise). My response was that I would be happy to review and testify to the fact that the SUPPORT trial was conducted to the highest ethical standards with the best knowledge available at the time and that the subjects were fortunate to have enrolled. I have not heard back from them.

If real experts cannot be found to testify to the false theory of causation and false breach of standard theory these people are propounding, there will be no case.

Henry J. Rozycki, M.D.
Division of Neonatal-Perinatal Medicine
Medical Director, Pediatric Research Office

Associate Professor of Pediatrics
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Ph: 804-828-9964
Fax: 804-828-6662
email: hrozycki@mcvh-vcu.edu

-----Forwarded by Henry Rozycki/Notes/MCVH on 06/06/2013 08:37AM -----

To: <hrozycki@mcvh-vcu.edu>
From: LCMT <lcmt@theexpertinstitute.com>
Date: 06/04/2013 03:50PM
Subject: Neonatal Case O-002671

Dr. Rozycki,

I hope you are having a great day. We have a new case that we need reviewed by an experienced neonatologist. Case details are below.

This case involves a class action suit taken up by the Federal Office for Human Research Protections which concluded that consent forms, used in a study of optimal oxygen saturation in premature infants, failed to reveal that there was a greater risk of dying in the low-oxygen group and a greater risk of severe eye damage in the high oxygen group. The consent form explicitly stated that, both groups would receive oxygen within the standard of care, and that there would be no predictable increase in risk no matter which randomized group the infant was in. The federal agency also found that many infants may have faced greater risks by participating, specifically, if a baby whose clinical needs might ordinarily have led doctors to deliver a relatively high level of oxygen was enrolled in the study, the infant might be randomly assigned to receive lower levels of oxygen. Additionally, the consent forms failed to sufficiently explain the potential risks of retinopathy of prematurity or death with using the experimental lower or higher oxygen saturation targets. All participating centers of this study had similar problems with their consent forms and the failure to disclose such critically important information directly affected parents' decisions to enroll their premature infants in this study.

An expert in Neonatology is needed to evaluate what individualized treatment of each premature infant would have looked like. For example, are there clinical signs or symptoms that are monitored during the course of treatment which would lead the treating doctor to decide whether to raise or lower the oxygen, or maintain the same level, on an ongoing basis? If that is the case, what research exists to show that such individualized care and treatment improves the outcomes?

If this is a case that you would be interested in reviewing, please provide me with your CV and fee schedule along with your answers to the questions above. Also, please let me know your litigation history (approximately how many cases you review per year, number of times being deposed, number of times at trial, percentage split between plaintiff and defense work).

If you have any questions about this case or how we work, please do not hesitate to give me a call on my direct line at 646.216.2338.

Best,

Zachary Barreto

VP of Litigation Support Services

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Fax: (302) 468 - 5295

Cell: (b)(6)

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From: Willinger, Marian (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NIMHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NEJM articles are now available
Date: Thursday, June 06, 2013 6:33:43 AM

This is (b)(5) In the end I think there will (b)(5)
(b)(5)

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 5:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NEJM articles are now available

Rose, great to (b)(5) We look forward to the Council Session tomorrow. Sleep well.

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
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Bethesda, MD 20892
Phone: 301-496-1848
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E-mail: maddoxy@mail.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 5:09 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: NEJM articles are now available
Importance: High

Thanks to all of you for your SUPPORT

http://www.nejm.org/doi/full/10.1056/NEJMp1306986?query=featured_home

http://www.nejm.org/doi/full/10.1056/NEJMc1307008?query=featured_home

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301-496-3790 (FAX)
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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Rich, Wade; mgantz@rti.org; "Duara, Shahnaz" (SDuara@med.miami.edu); moshea@wfubmc.edu; "Phelps, Dale"; Laroia, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6) hol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Vaucher, Yvonne; (Deanna_Maffett@urmc.rochester.edu); (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gauldin, Cheri.; Georgia McDavid; Holly_Wadkins@urmc.rochester.edu (Holly_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Thursday, June 06, 2013 6:05:02 AM

Hello Rose

Hopefully this signals the beginning of the end.

The support of the NIH and the current OHRP position are very positive steps.

I hope that we will all support Wally and UAB and play whatever role is necessary to help them deal with the current litigation process

Be well

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 05, 2013 11:05 PM
To: richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Rich, Wade; mgantz@rti.org; 'Duara, Shahnaz' (SDuara@med.miami.edu); Finer, Neil; moshea@wfubmc.edu; 'Phelps, Dale'; Laroia, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu);

(EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); drfjcmd@aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Vaucher, Yvonne; (Deanna_Maffett@urmc.rochester.edu); (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gauldin, Cheri,; Georgia McDavid; Holly_Wadkins@urmc. rochester. edu (Holly_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT ONLINE FIRST articles from this week's NEJM
Importance: High

http://www.nejm.org/doi/full/10.1056/NEJMp1306986?query=featured_home

http://www.nejm.org/doi/full/10.1056/NEJMc1307008?query=featured_home

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: WSJ: Sanction on Study Eased
Date: Wednesday, June 05, 2013 9:41:45 PM

Wall street journal--
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 09:37 PM
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Rockey, Sally (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Fritz, Craig (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Zuk, Dorit (NIH/OD) [E]; Tatem, Anne (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: WSJ: Sanction on Study Eased

Wall Street Journal
U.S. NEWS June 5, 2013, 7:38 p.m. ET

Sanction on Study Eased

By THOMAS M. BURTON

A federal agency that had criticized a study of oxygen given to premature infants said it was putting on hold any regulatory action against hospitals involved, saying that its rules could be misunderstood.

Hospitals and doctors had challenged the determination by the Office for Human Research Protections and defended the ethical standards of the study.

In a letter dated Tuesday to the University of Alabama at Birmingham, where the research was centered, Lisa R. Buchanan of the research office said that her agency was correct when it concluded in March that researchers didn't adequately notify parents of the possible risks in the study.

Related

Letter to the University of Alabama at Birmingham

But she said the office had an "obligation to provide clear guidance on what the rules are" and nodded to the views of those who disagreed with the office's initial finding.

At issue is a study of 1,300 premature babies, conducted between 2004 and 2009, that looked at the levels of oxygen they should receive. Too much oxygen could result in blindness, but too little, it turned out in the research, could result in excessive deaths.

About 28,000 infants weighing less than 2.75 pounds are born prematurely in the U.S. each year, and more than half develop a condition called retinopathy of prematurity, which often leads to blindness.

Many doctors in the study have said that they were surprised that babies on lower levels of oxygen had a higher death rate, and that they couldn't have warned of such an unexpected result.

Ms. Buchanan disagreed, writing: "Given the requirement that subjects be apprised of 'reasonably foreseeable risks,' it would seem appropriate that the parents of the infants should have been informed of the real concerns within the medical community regarding those oxygen levels."

On Wednesday, more than 30 senior physicians—including the director of the National Institutes of Health—spoke out in favor of the researchers.

In an opinion piece in the New England Journal of Medicine, NIH Director Francis Collins, along with NIH colleagues Kathy L. Hudson and Alan E. Guttmacher, wrote in support of the pediatricians' study. They said researchers "had no scientific evidence to expect a difference in mortality" between the two groups of babies. Both levels of oxygen at the time were considered within the standard of medical care.

In the study, among infants getting low oxygen, there was a higher percentage of deaths before discharge, 19.9%, compared with the 16.2% who died in the high oxygen group. The federal agency said this finding was "statistically significant." Among babies getting high oxygen levels, 17.9% got the severe

eye disease, compared with 8.6% who were treated with low oxygen.

Write to Thomas M. Burton at tom.burton@wsj.com

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nxs5@case.edu"
Subject: Re: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 9:37:23 PM

Wanted to keep everyone in the loop
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: nxs5@case.edu [mailto:nxs5@case.edu]
Sent: Wednesday, June 05, 2013 09:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT ONLINE FIRST articles from this week's NEJM

Wow Rose- those editorials were powerful! ....Nancy

Sent from my iPad

On Jun 5, 2013, at 5:04 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

http://www.nejm.org/doi/full/10.1056/NEJMp1306986?query=featured_home

http://www.nejm.org/doi/full/10.1056/NEJMc1307008?query=featured_home

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: D"Angio, Carl
To: "Barbara Stoll"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: " <richard.ehrenkranz@yale.edu>, Roger.Faix"@ws-mr1.cc.emory.edu
Subject: RE: SUPPORT ONLINE FIRST articles from this week's NEJM
Date: Wednesday, June 05, 2013 8:49:23 PM

I echo thanks to everyone at NICHD and NIH for their "support of SUPPORT."

Carl

Carl T. D'Angio, MD
Professor of Pediatrics and Medical Humanities & Bioethics
Director, Neonatal Clinical Research
Director, Pediatric Clinical Research Office
Director, Ethics Key Function, URMC CTSI
Division of Neonatology, Golisano Children's Hospital
University of Rochester Medical Center
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Wednesday, June 05, 2013 6:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: " <richard.ehrenkranz@yale.edu>, Roger.Faix"@ws-mr1.cc.emory.edu
Subject: Re: SUPPORT ONLINE FIRST articles from this week's NEJM

Thanks to Drs Collins, Guttmacher and Hudson

AND thanks to Rose-- for fostering an open dialogue and helping all of the NRN investigators weather this difficult period

BSJ**"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:**

http://www.nejm.org/doi/full/10.1056/NEJMp1306986?query=featured_home

http://www.nejm.org/doi/full/10.1056/NEJMe1307008?query=featured_home

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please notify the sender immediately and delete the original.

Blansfield, Earl (NIH/NICHD) [E]

From:	Guttmacher, Alan (NIH/NICHD) [E]
Sent:	Wednesday, June 05, 2013 8:26 PM
To:	Barbara Stoll
Cc:	Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]
Subject:	Re: SUPPORT Editorial--ONLINE FIRST articles from this week's NEJM

Barbara -

Thanks for the much appreciated note. We - the research community and research participants - are all in this together. Let's hope we take good advantage of this teachable moment.

Best, Alan

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On Jun 5, 2013, at 6:51 PM, "Barbara Stoll" <Barbara.Stoll@oz.ped.emory.edu> wrote:

> Thanks to each of your for your thoughtful and important editorial in the NEJM today.
>
> As you so eloquently write, the issues surrounding this trial have implications far beyond SUPPORT.
>
> A special thank you to our wonderful Neonatal Network Project Officer, Rose Higgins, who has facilitated an open dialogue and helped the PIs weather this difficult period.
>
> Regards
> BJS
>
> Barbara J. Stoll, MD
> George W. Brumley, Jr., Professor and Chair
> Department of Pediatrics, Emory University School of Medicine
> President and CEO, Emory-Children's Center
> SVP and Chief Academic Officer, Children's Healthcare of Atlanta
> 2015 Uppergate Dr
> Atlanta GA 30322
> Office: 404-727-2456 Fax: 404-727-5737
> barbara_stoll@oz.ped.emory.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 8:07:49 PM

Good luck!
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, June 05, 2013 07:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT ONLINE FIRST articles from this week's NEJM

My flight is delayed and I will arrive at about 10.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Wed, Jun 5, 2013 23:12:17 GMT+00:00
Subject: Re: SUPPORT ONLINE FIRST articles from this week's NEJM

Wally
Thank YOU for all the support!
See you in the am.
When does your flight leave in the afternoon?
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, June 05, 2013 06:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; Roger Faix (Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Wade RIch <wrich@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; 'Duara, Shahnaz' (SDuara@med.miami.edu) <SDuara@med.miami.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; 'Phelps, Dale' <Dale_Phelps@URMC.Rochester.edu>; Laroia, Nirupama <Nirupama_Laroia@URMC.Rochester.edu>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; Frantz, Ivan <Ivan.Frantz@childrens.harvard.edu>; (suhas.kallapur@cchmc.org) <suhas.kallapur@cchmc.org>; Abbot Laptook (alaptook@wihri.org) <alaptook@wihri.org>; Abhik Das (adas@rti.org) <adas@rti.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu) <AnnaMaria.hibbs@cwru.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@URMC.Rochester.edu>; Carlton, David P <dpcarlt@emory.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>;

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "kwatterberg@salud.unm.edu"
Subject: Re: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 7:21:55 PM

Thank you for your kind comment

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Wednesday, June 05, 2013 07:11 PM
To: (b)(6) @aol.com (b)(6) @aol.com>; Satyan Lakshminrusimha <slakshmi@buffalo.edu>; Kim Yolton <kimberly.yolton@cchmc.org>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; (suhas.kallapur@cchmc.org) <suhas.kallapur@cchmc.org>; (Vivek.Narendran@cchmc.org) <Vivek.Narendran@cchmc.org>; Ivan Frantz <Ivan.Frantz@childrens.harvard.edu>; Cheri Gauldin <cagauldin@cmh.edu>; Howard Kilbride (hkilbride@cmh.edu) <hkilbride@cmh.edu>; William (MD) Truog <wtruog@cmh.edu>; Anna Maria Hibbs(AnnaMaria.hibbs@cwru.edu) <AnnaMaria.hibbs@cwru.edu>; Nancy Newman <nxs5@cwru.edu>; Kimberley Fisher <Kimberley.fisher@duke.edu>; Marsha Gerdes (gerdes@email.chop.edu) <gerdes@email.chop.edu>; Hallam Hurt (hurt@email.chop.edu) <hurt@email.chop.edu>; Haresh Kirpalani (KIRPALANIH@email.chop.edu) <KIRPALANIH@email.chop.edu>; David P Carlton <dpcarlt@emory.edu>; Ellen Hale (ehale@emory.edu) <ehale@emory.edu>; ira adams-chapman <iadamsc@emory.edu>; Rachel Geller <rgeller.mednet.ucla@gmail.com>; Brad Yoder(Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Roger Faix(Roger.Faix@hsc.utah.edu) <Roger.Faix@hsc.utah.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Diane Wilson <dhwilson@iupui.edu>; Greg Sokol (gsokol@iupui.edu) <gsokol@iupui.edu>; Leslie Wilson <ldw@iupui.edu>; Bethany Ball <mbball@leland.stanford.edu>; Richard Polin <rap32@mail.cumc.columbia.edu>; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; golds005@mc.duke.edu <golds005@mc.duke.edu>; Shahnaz'(SDuara@med.miami.edu) 'Duara <SDuara@med.miami.edu>; John Barks <jbarks@med.umich.edu>; Martha Colson <marthac@med.umich.edu>; Stephanie Wiggins <shigdon@med.umich.edu>; (apappas@med.wayne.edu) <apappas@med.wayne.edu>; Beena [bsood@med.wayne.edu] Sood <bsood@med.wayne.edu>; Becky Bara <rbara@med.wayne.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Isabell Purdy(ipurdy@mednet.ucla.edu) <ipurdy@mednet.ucla.edu>; Meena Garg(mgarg@mednet.ucla.edu) <mgarg@mednet.ucla.edu>; Rachel Geller <rgeller@mednet.ucla.edu>; Teresa Chanlaw (tchanlaw@mednet.ucla.edu) <tchanlaw@mednet.ucla.edu>; UdayDevaskar (UDEVASKAR@MEDNET.UCLA.EDU) <UDEVASKAR@mednet.ucla.edu>; Christine Fortney <Christine.Fortney@nationwidechildrens.org>; Keith Yeates(Keith.Yeates@nationwidechildrens.org) <Keith.Yeates@nationwidechildrens.org>; Leif Nelin <Leif.Nelin@nationwidechildrens.org>; Joanne Finkel <JF126@notes.duke.edu>; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; Monica Collins <mcollins@peds.uab.edu>; MyriamPeralta-Carcelen (MPeralta@peds.uab.edu) <MPeralta@peds.uab.edu>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; Abhik Das (adas@rti.org) <adas@rti.org>; dwallace@rti.org <dwallace@rti.org>; mgantz@rti.org <mgantz@rti.org>; Andrea Duncan <AFDuncan@salud.unm.edu>; Conra Lacy <CBackstrom@salud.unm.edu>; Janell Fuller <JaFuller@salud.unm.edu>; Robin Ohls <ROhls@salud.unm.edu>; dstevenson@stanford.edu <dstevenson@stanford.edu>; Susan Hintz <srhintz@stanford.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; (EMcGowan@tufts-nemc.org) <EMcGowan@tufts-nemc.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; WallyCarlo (wacarlo@uab.edu) <wacarlo@uab.edu>; Cathy Grisby (cathy.grisby@uc.edu) <cathy.grisby@uc.edu>; Jean Steichen(steichjj@uc.edu) <steichjj@uc.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Wade RIch <wrich@ucsd.edu>; Yvonne Vaucher <yvaucher@ucsd.edu>; Allison Payne <Allison.Payne@UHhospitals.org>; Donia Campbell <donia-campbell@uiowa.edu>; Ed Bell(edward-bell@uiowa.edu) <edward-bell@uiowa.edu>; Karen Johnson (karen-johnson@uiowa.edu) <karen-

johnson@uiowa.edu>; Tarah Colaizy (tarah-colaizy@uiowa.edu) <tarah-colaizy@uiowa.edu>; (kwynn@upa.chob.edu) <kwynn@upa.chob.edu>; Aasma Chaudhary(aasma.chaudhary@uphs.upenn.edu) <aasma.chaudhary@uphs.upenn.edu>; Barbara (Neonatology) Schmidt <barbara.schmidt@uphs.upenn.edu>; Soraya Abbasi(soraya.abbasi@uphs.upenn.edu) <soraya.abbasi@uphs.upenn.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@urmc.rochester.edu>; Dale' 'Phelps <Dale_Phelps@urmc.rochester.edu>; (Deanna_Maffett@urmc.rochester.edu) <Deanna_Maffett@urmc.rochester.edu>; Gary Myers (gary_myers@URMC.Rochester.edu) <gary_myers@urmc.rochester.edu>; Holly_Wadkins@urmc. rochester. edu (Holly_Wadkins@urmc.rochester.edu) <Holly_Wadkins@urmc.rochester.edu>; Linda Reubens <linda_reubens@urmc.rochester.edu>; Nirupama Laroia <Nirupama_Laroia@urmc.rochester.edu>; ronnie_guillet@urmc.rochester.edu <ronnie_guillet@urmc.rochester.edu>; Rosemary Jensen (Rosemary_Jensen@urmc.rochester.edu) <Rosemary_Jensen@urmc.rochester.edu>; Georgia McDavid <Georgia.E.McDavid@uth.tmc.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kathleen A Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>; PatrickJones <Patrick.M.Jones@uth.tmc.edu>; DianaVasil <Diana.Vasil@UTSouthwestern.edu>; Lijun Chen (Lijun.Chen@UTSouthwestern.edu) <Lijun.Chen@UTSouthwestern.edu>; Luc Brion (luc.brion@utsouthwestern.edu) <luc.brion@UTSouthwestern.edu>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; Roy Heyne <Roy.Heyne@UTSouthwestern.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; AngelitaHensman <ahensman@wihri.org>; Abbot Laptook(alaptook@wihri.org) <alaptook@wihri.org>; BettyVohr (bvohr@wihri.org) <bvohr@wihri.org>; Martin Keszler (mkeszler@wihri.org) <mkeszler@wihri.org>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT ONLINE FIRST articles from this week's NEJM

WONDERFUL NEWS! Thanks for your continuing leadership ~ Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 6/5/2013 3:04 PM >>>

http://www.nejm.org/doi/full/10.1056/NEJMp1306986?query=featured_home

http://www.nejm.org/doi/full/10.1056/NEJMc1307008?query=featured_home

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Barbara.Stoll@oz.ped.emory.edu"
Subject: Re: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 7:21:38 PM

Thanks for your support

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Wednesday, June 05, 2013 06:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: " <richard.ehrenkranz@yale.edu>, " Roger.Faix@ws-mr1.cc.emory.edu <"
<richard.ehrenkranz@yale.edu>, " Roger.Faix@ws-mr1.cc.emory.edu>
Subject: Re: SUPPORT ONLINE FIRST articles from this week's NEJM

Thanks to Drs Collins, Guttmacher and Hudson

AND thanks to Rose-- for fostering an open dialogue and helping all of the NRN investigators weather this difficult period

BSJ**"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:**

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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 7:05:36 PM

Thanks Rose. When the dust finally settles, this whole debacle will have clarified many issues.

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 05, 2013 2:05 PM
To: richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Rich, Wade; mgantz@rti.org; 'Duara, Shahnaz' (SDuara@med.miami.edu); Finer, Neil; moshea@wfubmc.edu; 'Phelps, Dale'; Laroia, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); drfjcmd@aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Vaucher, Yvonne; (Deanna_Maffett@urmc.rochester.edu); (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gauldin, Cheri,; Georgia McDavid; Holly_Wadkins@urmc. rochester. edu (Holly_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT ONLINE FIRST articles from this week's NEJM
Importance: High

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From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 6:21:26 PM

Now I know what you were talking about this morning!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, June 05, 2013 05:05 PM Eastern Standard Time
To: richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Wade RIch; Gantz, Marie; 'Duara, Shahnaz' (SDuara@med.miami.edu); nfiner@ucsd.edu; moshea@wfubmc.edu; 'Phelps, Dale'; Laroia, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Das, Abhik; Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); [SCRN] Stoll, Barbara; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; Wallace, Dennis; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); drfjcmd@aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; (Deanna_Maffett@urmc.rochester.edu); (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gauldin, Cheri,; Georgia McDavid; Holly_Wadkins@urmc. rochester. edu (Holly_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT ONLINE FIRST articles from this week's NEJM

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Wade RIch; mgantz@rti.org; "Duara, Shahnaz" (SDuara@med.miami.edu); nfiner@ucsd.edu; moshea@wfubmc.edu; "Phelps, Dale"; Laroia, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); drfjcmd@aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); Ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichji@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta, M.D.; Patrick Jones; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; (Deanna_Maffett@urmc.rochester.edu); (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gauldin, Cheri.; Georgia McDavid; Holly_Wadkins@urmc. rochester. edu (Holly_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: SUPPORT ONLINE FIRST articles from this week"s NEJM
Date: Wednesday, June 05, 2013 6:15:35 PM

Rose.

Thanks to you and the NIH leadership for the unconditional support.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "Roger Faix (Roger.Faix@hsc.utah.edu)" <Roger.Faix@hsc.utah.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, Wade RIch <wrich@ucsd.edu>, "mgantz@rti.org" <mgantz@rti.org>, "'Duara, Shahnaz' (SDuara@med.miami.edu)" <SDuara@med.miami.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "moshea@wfubmc.edu" <moshea@wfubmc.edu>, "'Phelps, Dale'" <Dale_Phelps@URMC.Rochester.edu>, "Laroia, Nirupama" <Nirupama_Laroia@URMC.Rochester.edu>, " (Vivek.Narendran@cchmc.org)" <Vivek.Narendran@cchmc.org>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "Frantz, Ivan" <Ivan.Frantz@childrens.harvard.edu>, " (suhas.kallapur@cchmc.org)" <suhas.kallapur@cchmc.org>, "Abbot Laptook (alaptook@wihri.org)" <alaptook@wihri.org>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Anna Maria Hibbs

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Cc: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>
Sent: Wed, Jun 5, 2013 21:05:43 GMT+00:00
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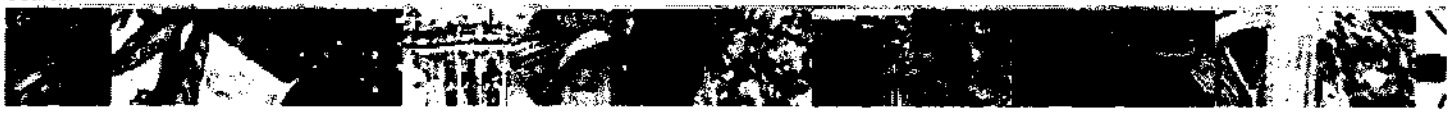
Blansfield, Earl (NIH/NICHD) [E]

From: Burklow, John (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 5:34 PM
To: Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Alexander, Rashada (NIH/OD) [E]
Subject: Emailing: In Support of SUPPORT — A View from the NIH — NEJM.htm

Looks nice! Congratulations!



PERSPECTIVE

In Support of SUPPORT — A View from the NIH

Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

June 5, 2013DOI: 10.1056/NEJMp1306986

Each year in the United States, nearly 500,000 infants — 1 in every 8 — are born prematurely, before 37 weeks of gestation. Despite substantial advances in their care, premature infants face a daunting array of challenges; they are at high risk for death in infancy and face severe and lifelong health problems if they survive.1 The National Institutes of Health (NIH) has a legal and moral responsibility to do research in partnership with scientists and families to optimize the care of these highly vulnerable infants. In recent weeks, a major public debate has arisen regarding a study designed to do just that. And the ramifications go well beyond this one study: the outcome of this debate could affect how we conduct and communicate about critical research on interventions that are within the standard of care for all diseases and conditions.

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), carried out at more than 20 sites between 2004 and 2009, sought to identify, in infants born very prematurely at 24 to 27 weeks' gestation, the oxygen-saturation level within the range considered the standard of care that would minimize the risk of retinopathy of prematurity (ROP), a complication of oxygen therapy that can result in vision loss.2 When the study began, targeting an oxygen-saturation range of 85 to 95% was becoming standard clinical practice, and the American Academy of Pediatrics (AAP) later recommended this range in its 2007 guidelines. The SUPPORT researchers and institutional review boards (IRBs), practicing clinicians, and the AAP had no scientific evidence to expect a difference in mortality between the two treatment groups in SUPPORT — one with the oxygen saturation target of 85 to 89%, the other with the target of 91 to 95%.

An important finding of the study was a reduced incidence of ROP in the lower oxygen-saturation range. However, contrary to what was known at the time, the study also showed a slightly but significantly increased incidence of death — 19.9% versus 16.2% (P=0.04) — among infants assigned to the lower as compared with the upper range. As a result, last year the AAP amended its guidelines, citing SUPPORT, and physicians treating very premature infants are starting to use higher saturation rates to reduce the risk of death, even with the potentially higher risk of ROP at these levels. Studies such as SUPPORT that compare two alternatives, both within current standard clinical practice, often lead to critical improvements in medical care.

A 400-Gram Female Infant Delivered at 24 and 4/7 Weeks.

The federal Office for Human Research Protections (OHRP), which is charged with providing leadership in the protection of the rights, welfare, and well-being of persons involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS), asserted in March 2013, on the basis of its own examination of the evidence, that the SUPPORT researchers failed to provide prospective parents sufficient information about the risks posed by the study. After a detailed review of the protocol, the relevant consent documents, and the research literature, we respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPORT study commenced. Moreover, there is a larger issue here: how risks should be conveyed in the informed-consent process when research is comparing interventions that are all considered to be the standard of care.

In a letter dated March 7, 2013, the OHRP asserted that the study's consent form failed to convey that "the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death."[3] That finding was influenced by research conducted in the 1950s, but in our view, it failed to assign proper weight to studies conducted in premature infants in the 2000s, which used more sophisticated oxygen-monitoring and oxygen-measurement devices, similar to those used in SUPPORT.[4] The more recent studies showed no increased risk of death or neurodevelopmental impairment at saturation levels as low as 70%.[5]

Given these data, the investigators had no reason to foresee that infants in one study group would have a higher risk of death than would those in the other group. The babies included in SUPPORT were, of course, facing substantial risks because of prematurity — the same risks as premature babies who were not enrolled in the study — but their care was never compromised for the sake of the study. The sample consent form for SUPPORT stated that each of the "possible combinations of treatments is considered by some units to represent their desired approach" (www.nih.gov/icd/od/foia/library/Records.htm). This statement describes the clinical equipoise at the time of the study, which was, in fact, the justification for conducting a clinical trial. Although the OHRP took issue with the consent form, it stated that the study design was ethical — a conclusion worth emphasizing. The increased risk of death was a significant and unexpected finding of the study; if it had been known before the study began, standard clinical care would not have encompassed the lower oxygen range, and it would have been unethical to conduct the study.

The NIH is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. We are strongly committed to supporting critical research studies like SUPPORT, which inform clinical care by providing rigorous evidence for use in daily practice. This controversy has alarmed some of the parents of infants who were in the study, confused the biomedical research community, and befuddled IRBs. Several other studies seeking new insights to improve care for these vulnerable infants have been put on hold as the field tries to understand the OHRP findings.

But controversies such as this are also an opportunity to advance shared understanding, provide clarification, and encourage progress. The public debate surrounding the SUPPORT study has set the stage for a substantive national dialogue with the research, advocacy, and ethics communities on how best to respect and protect participants in research studies conducted within the standard of care and how to define "reasonably foreseeable risks" in this setting. The timing is critical — the clinical research community, bioethicists, regulators, IRBs, and prospective research participants are paying close attention now. The NIH is happy to work with all stakeholders to advance this important dialogue and its translation into clear guidance, in accordance with the plan just announced by the DHHS (www.hhs.gov/ohrp/). In addition, a new letter to the University of Alabama at Birmingham from the OHRP, stating its intention to put all compliance actions on hold until the process of producing appropriate guidance is completed, is available now on the OHRP website (www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf).

Going forward, the NIH strongly and unequivocally supports the importance of the role of the OHRP in the oversight of human subjects research. But the community will benefit from an explicit description of the process the OHRP follows for investigating complaints. For example, when questions are raised about reasonably foreseeable risks and the state of the science relevant to a particular clinical trial, appropriate independent experts might need to be consulted. Finally, we are pleased to see the DHHS plans to ensure that investigators and IRBs will have a fair and transparent process for

appealing OHRP findings and compliance actions, in those situations in which reasonable people disagree about the actions taken.

The circumstances surrounding the SUPPORT study have unquestionably created controversy in the research community, but the situation has created an opportunity for a better understanding of the scientific and ethical issues that must be addressed when designing such studies in the future. We look forward to working with the OHRP, the research community, and patient advocates to improve the effectiveness and ethical standards of research involving human participants.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article was published on June 5, 2013, at NEJM.org.

Source Information

From the National Institutes of Health, Bethesda, MD.

References

REFERENCES

1. 1

Martin JA, Hamilton BE, Ventura SJ, Osteman MJK, Wilson EC, Mathews TJ. Births: final data for 2010. Natl Vital Stat Rep 2012;61:1-71 (http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_01.pdf)

2. 2

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-1969
Free Full Text | Web of Science | Medline

3. 3

Determination Letter from the Office for Human Research Protections to University of Alabama at Birmingham. March 7, 2013 (http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf)

4. 4

Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003;111:339-345
CrossRef | Web of Science | Medline

5. 5

Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-F110
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From: Spong, Catherine (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Re: NEJM articles are now available
Date: Wednesday, June 05, 2013 5:18:38 PM

This is great! Thanks and congratulations to all!

Catherine Y Spong MD
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On Jun 5, 2013, at 5:11 PM, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov> wrote:

> Attached as PDFs. Also, here are the urls for the OHRP letter and the HHS statement
>
> This is the link for OHRP letter to UAB:
> http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf
>
> This is the link announcing public meeting:
> http://www.hhs.gov/ohrp/
> (meeting notice will be on front page until August)
>
> Way to go team!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
>
> Alan
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [E]
> Sent: Wednesday, June 05, 2013 5:09 PM
> To: Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
> Subject: NEJM articles are now available
> Importance: High
>
> Thanks to all of you for your SUPPORT
>
> http://www.nejm.org/doi/full/10.1056/NEJMp1306986?query=featured_home
>
>
>
> http://www.nejm.org/doi/full/10.1056/NEJMc1307008?query=featured_home
>
>
>
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> <NIH Perspective.pdf>
> <Wilfond-Magnus Letter.pdf>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: FW: OHRP letter
Date: Wednesday, June 05, 2013 4:24:00 PM

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, June 05, 2013 2:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: OHRP letter

I guess it has already leaked:

http://tinyurl.com/OHRP-SUPPORT

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: AHRP/ OHRP Caves Under SUPPORT Pressure
Date: Wednesday, June 05, 2013 2:48:00 PM
Importance: High

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-----Original Message-----
From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 2:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: AHRP/ OHRP Caves Under SUPPORT Pressure
Importance: High

In case you didn't see --the other side is coming out -- should be an interesting time in the media

-----Original Message-----
From: AHRP [mailto:ahrp@ahrp.org]
Sent: Wednesday, June 05, 2013 2:07 PM
To: Infomail1@ahrp.org
Subject: OHRP Caves Under SUPPORT Pressure Re: oxygen experiment tiny premature babies
Importance: High

ALLIANCE FOR HUMAN RESEARCH PROTECTION (AHRP) Advancing Honest and Ethical Medical Research
www.ahrp.org

FYI

BEWARE of the powerful influence of institutional medical research.

They have pushed hard to get the federal research oversight agency, OHRP, to backtrack from its oversight action after determining that there was an institutional failure of compliance with Federal regulatory requirements by medical centers that conducted the SUPPORT oxygen supplementation experiment in premature babies. [http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf]

In a letter to the the University of Alabama (May 4, 2013), OHRP is alerting the public that powerful forces are intent on lowering the bar for medical research ethics.
Excerpts at: http://www.ahrp.org/cms/content/view/924/9/

"Ultimately the issues come down to fundamental difference between the obligations of clinicians and those of researchers. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same
obligation: Our society relaxes that requirement because of the need to conduct research, the result of which are important to us all. As a trade-off in allowing researchers such flexibility, society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed."

OHRP does reamin steadfast in its finding that the SUPPORT consent forms failed to disclose the increased risk of death:
"it would seem appropriate that the parents of the infants should have been informed of the real concerns withing the medical community regarding those [high and low end of] oxygen levels" to which babies may be randomly assigned in the study.

Lest anyone have any doubt about the ultimate goal of the powerful government-sponsored researchers who conduct high risk experiments, OHRP notes that:

"some of the researchers involved in the SUPPORT study and others have argued that there was no need for researchers to have obtained any consent from parents before placing their children in this study."

This discussion takes place in the midst of a much broader discussion regarding a proposal from a distinguished group of scholars that is receiving prominent attention, which argues for completely eliminating the need for any consent in similar studies."

"These are crucially important issues, not just with regard to our ability to be able to conduct research with appropriate oversight, but also with regard to fundamental questions about the obligations owed by doctors to patients."

"Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing guidance [on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care] is as open as possible, to allow input from all interested parties."

OHRP promises to conduct an open public meeting on this topic.

In the meantime, OHRP has "put on hold all compliance actions against UAB to the SUPPORT case, and plan to take no further action in studies involving similar designs until the process of producing appropriate guidance is completed."

Take action to prevent a return to pre-Nuremberg medical research standards when medical atrocities were committed "for the greater good."

We, the 99.9% are at increasingly high risk of becoming human guinea pigs without our informed consent.

Vera Sharav

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michele Walsh (mcw3@cwru.edu); Pablo.Sanchez@UTSouthwestern.edu; "Duara, Shahnaz" (SDuara@med.miami.edu); barbara_stoll@oz.ped.emory.edu; Kurt Schibler [kurt.schibler@cchmc.org]; Poindexter, Brenda B (bpoindex@iu.edu); richard.ehrenkranz@yale.edu; Abbot Laptook; Krisa Van Meurs (vanmeurs@stanford.edu); Wally Carlo; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; nfiner@ucsd.edu; Bell, Edward (Pediatrics); Frantz, Ivan; Roger Faix (Roger.Faix@hsc.utah.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu; Phelps, Dale; (Vivek.Narendran@cchmc.org); Wade Rich; mgantz@rti.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Abhik Das (adas@rti.org); nxs5@case.edu; Ambal (ambal@uab.edu); brenda_2759@msn.com; Laroia, Nirupama; Sood, Beena; moshea@wfubmc.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org); Schmidt, Barbara (Neonatology); Truog, William (MD); Uday Devaskar (udevaskar@mednet.ucla.edu); Nelin, Leif
Subject: Re: Follow up letter
Date: Wednesday, June 05, 2013 12:57:56 PM

Rose
I just wanted to say that my impression of cite 9 (page 5) was not getting antenatal consent results in a cohort that is not generalizable----
Seetha

Sent from my iPhone

On Jun 5, 2013, at 11:59 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> A follow up letter – let me know if you would like to have a steering committee call sooner than 6/25.
>
> Rose
>
> <DCOI U Ala Birmingham 060413 signed (2).pdf>

From: Spong, Catherine (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT pdf proof and new photo
Date: Wednesday, June 05, 2013 12:40:10 PM

(b)(5)

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On Jun 5, 2013, at 11:55 AM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

> Hi Stephanie – I told them highly unlikely that we could get a picture with a higher resolution –but they asked me to ask anyway –
>
> My sense is that (b)(5)
> (b)(5)
>
> Rose/Cathy- I am hesitant to go back to the well again? Want to give me a call?
>
> *Mona*
>
> Mona Jaffe Rowe, M.C.P.
> Associate Director for Science Policy,
> Analysis and Communication
> *Eunice Kennedy Shriver* National Institute of
> Child Health and Human Development
> National Institutes of Health, DHHS
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From: Devaney, Stephanie (NIH/OD) [E]

Sent: Wednesday, June 05, 2013 11:42 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT pdf proof and new photo

If you could just ask, I'll let Debbie know that it's unlikely. Thanks, Mona

---

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 11:40 AM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: SUPPORT pdf proof and new photo

I think that is all we had – the investigator took it herself – we can check - -but I think that it is highly unlikely we can get a different one—what is the time frame?

Mona

Mona Jaffe Rowe, M.C.P.
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From: Devaney, Stephanie (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 11:38 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: SUPPORT pdf proof and new photo
Importance: High

Hi Mona –

See the email from NEJM below – do we have a better resolution photo? She has the version attached that you sent last night.

Thank you!
Steph

From: Moskowitz, Deborah [mailto:dmoskowitz@nejm.org]
Sent: Wednesday, June 05, 2013 11:30 AM
To: Devaney, Stephanie (NIH/OD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]

Subject: RE: SUPPORT pdf proof and new photo
Importance: High

Do you have a version of this photo with better resolution? The resolution on this is not great, and the Medical Illustrations team would prefer better resolution.

Thanks!
--Debbie

From: Devaney, Stephanie (NIH/OD) [E] [mailto:stephanie.devaney@nih.gov]
Sent: Wednesday, June 05, 2013 7:00 AM
To: Moskowitz, Deborah
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: SUPPORT pdf proof and new photo

Hi Debbie –

Everyone looked over the proofs you sent along and we had just a couple changes, which I've included in the attached. I marked it up using the note bubbles in adobe. Will this work?

Also, we have a new photo with a caption that we'd like to use. The parents signed a consent for use in this article so we'd really like to use this one. That is attached and pasted here.

Thank you for all of your help. Please let me know if you need anything further.

Best,
Stephanie

<image001.jpg>

Short caption: A 400-gram female infant delivered at 24 and 4/7 weeks.

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Follow up letter
Date: Wednesday, June 05, 2013 12:33:06 PM

No: not needed. Didn't see anything in NEJM today.

Michele Walsh
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Rainbow Babies & Childrens Hospital
Professor of Pediatrics
Case Western Reserve University
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Cleveland, OH 44106-6010
email: michele.walsh@cwru.edu
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Fax: (216) 844-3380

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 05, 2013 11:58 AM
To: Michele Walsh (mcw3@cwru.edu); Pablo.Sanchez@UTSouthwestern.edu; Seetha Shankaran ; 'Duara, Shahnaz' (SDuara@med.miami.edu); barbara_stoll@oz.ped.emory.edu; Kurt Schibler [kurt.schibler@cchmc.org]; Poindexter, Brenda B (bpoindex@iu.edu); richard.ehrenkranz@yale.edu; Abbot Laptook; Krisa Van Meurs (vanmeurs@stanford.edu); Wally Carlo; Kennedy, Kathleen A; Jon.E.Tyson@uth.tmc.edu; goldb008@mc.duke.edu; cotte010@mc.duke.edu; nfiner@ucsd.edu; 'Bell, Edward (Pediatrics)'; Frantz, Ivan; Roger Faix (Roger.Faix@hsc.utah.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); carl_dangio@urmc.rochester.edu; 'Phelps, Dale'; (Vivek.Narendran@cchmc.org); Wade RIch; mgantz@rti.org; Brad Yoder (Bradley.yoder@hsc.utah.edu); Abhik Das (adas@rti.org); nxs5@case.edu; Ambal (ambal@uab.edu); brenda_2759@msn.com; Laroia, Nirupama; Sood, Beena [bsood@med.wayne.edu]; moshea@wfubmc.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org); Schmidt, Barbara (Neonatology); Truog, William (MD); Uday Devaskar (udevaskar@mednet.ucla.edu); Nelin, Leif
Subject: Follow up letter

A follow up letter – let me know if you would like to have a steering committee call sooner than 6/25.

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT pdf proof and new photo
Date: Wednesday, June 05, 2013 12:16:00 PM

I just tried and her cell _ I will shot her an email

Rosemary D. Higgins, MD
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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 12:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT pdf proof and new photo

Need me to call Brenda?

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 11:55 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: SUPPORT pdf proof and new photo
Importance: High

Hi Stephanie – I told them highly unlikely that we could get a picture with a higher resolution –but they asked me to ask anyway –

My sense is that Brenda took the picture with an iPhone or some readily available device and it might be impossible to get a higher resolution picture.. I really don't want to ask Brenda to take another picture - -probably also impossible to get better resolution without different equipment.

Rose/Cathy- I am hesitant to go back to the well again? Want to give me a call?

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 11:42 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT pdf proof and new photo

If you could just ask, I'll let Debbie know that it's unlikely. Thanks, Mona

---

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 11:40 AM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: SUPPORT pdf proof and new photo

I think that is all we had – the investigator took it herself – we can check - -but I think that it is highly unlikely we can get a different one—what is the time frame?

Mona

Mona Jaffe Rowe, M.C.P.
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Analysis and Communication
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Email: rowem@mail.nih.gov

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 11:38 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: SUPPORT pdf proof and new photo
Importance: High

Hi Mona –

See the email from NEJM below – do we have a better resolution photo? She has the version attached that you sent last night.

Thank you!
Steph

From: Moskowitz, Deborah [mailto:dmoskowitz@nejm.org]
Sent: Wednesday, June 05, 2013 11:30 AM
To: Devaney, Stephanie (NIH/OD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: RE: SUPPORT pdf proof and new photo
Importance: High

Do you have a version of this photo with better resolution? The resolution on this is not great, and the Medical Illustrations team would prefer better resolution.

Thanks!
--Debbie

From: Devaney, Stephanie (NIH/OD) [E] [mailto:stephanie.devaney@nih.gov]
Sent: Wednesday, June 05, 2013 7:00 AM
To: Moskowitz, Deborah
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: SUPPORT pdf proof and new photo

Hi Debbie –

Everyone looked over the proofs you sent along and we had just a couple changes, which I've included in the attached. I marked it up using the note bubbles in adobe. Will this work?

Also, we have a new photo with a caption that we'd like to use. The parents signed a consent for use in this article so we'd really like to use this one. That is attached and pasted here.

Thank you for all of your help. Please let me know if you need anything further.

Best,
Stephanie

Short caption: A 400-gram female infant delivered at 24 and 4/7 weeks.

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, June 05, 2013 10:15 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Glavin, Sarah (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Another controversial OHRP ruling on NCI study
Attachments: NCI vinegar study.docx

Please note the attached article that Sarah found – She highlighted in yellow where the article discusses how OHRP made a controversial ruling on this important trial – an off-base ruling with which the experts and researchers also disagreed. Seems like an (b)(5)

Mona

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See attached – text relating to bioethics is highlighted.

Sarah

Sarah L. Glavin, Ph.D.
Deputy Director
Office of Science Policy, Analysis and Communication
Chief, Science Policy, Planning and Evaluation Branch
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www.nichd.nih.gov

The Washington Post

Back to previous page

Study: Cheap vinegar test cut cervical cancer deaths in India; could help many poor countries

By Associated Press, Published: June 2

MUMBAI, India — A simple vinegar test slashed cervical cancer death rates by one-third in a remarkable study of 150,000 women in the slums of India, where the disease is the top cancer killer of women.

Doctors reported the results Sunday at a cancer conference in Chicago. Experts called the outcome "amazing" and said this quick, cheap test could save tens of thousands of lives each year in developing countries by spotting early signs of cancer, allowing treatment before it's too late.

Usha Devi, one of the women in the study, says it saved her life.

"Many women refused to get screened. Some of them died of cancer later," Devi said. "Now I feel everyone should get tested. I got my life back because of these tests."

Pap smears and tests for HPV, a virus that causes most cervical cancers, have slashed cases and deaths in the United States. But poor countries can't afford those screening tools.

This study tried a test that costs very little and can be done by local people with just two weeks of training and no fancy lab equipment. They swab the cervix with diluted vinegar, which can make abnormal cells briefly change color.

This low-tech visual exam cut the cervical cancer death rate by 31 percent, the study found. It could prevent 22,000 deaths in India and 72,600 worldwide each year, researchers estimate.

"That's amazing. That's remarkable. It's a very exciting result," said Dr. Ted Trimble of the National Cancer Institute in the U.S., the main sponsor of the study.

The story of research participant Usha Devi is not an unusual one. Despite having given birth to four children, she had never had a gynecological exam. She had been bleeding heavily for several years, hoping patience and prayers would fix things.

"Everyone said it would go away, and every time I thought about going to the doctor there was either no money or something else would come up," she said, sitting in a tiny room that serves as bedroom, kitchen, bathroom and living room for her entire family.

One day she found a card from health workers trying to convince women to join the study. Devi is in her late 40s and like many poor Indians doesn't know her date of birth. She learned she had advanced cervical cancer. The study paid for surgery to remove her uterus and cervix.

The research effort was led by Dr. Surendra Shastri of Tata Memorial Hospital in Mumbai. India has nearly one-third of the world's cases of cervical cancer — more than 140,000 each year.

"It's just not possible to provide Pap smear screening in developing countries. We don't have that kind of money" or the staff or equipment, so a simpler method had to be found, Shastri said.

Starting in 1998, researchers enrolled 75,360 women to be screened every two years with the vinegar test. Another 76,178 women were chosen for a control, or comparison group that just got cancer education at the start of the study and vouchers for a free Pap test — if they could get to the hospital to have one. Women in either group found to have cancer were offered free treatment at the hospital.

Still, this quick and free cancer screening was a hard sell in a deeply conservative country where women are subservient and need permission from husbands, fathers or others for even routine decisions. Social workers were sent into the slums to win people over.

"We went to every single house in the neighborhood assigned to us introducing ourselves and asking them to come to our health talks. They used to come out of curiosity, listen to the talk but when we asked them to get screened they would totally refuse," said one social worker, Vaishnavi Bhagat. "The women were both scared and shy."

One woman who did agree to testing jumped up from the table when she was examined with a speculum. "She started screaming that we had stolen her kidney," Bhagat said. Another health worker was beaten by people in the neighborhood when women realized they would have to disrobe to be screened.

"There was a sense of shame about taking their clothes off. A lot of them had their babies at home and had never been to a doctor," said one health worker, Urmila Hadkar. "Sometimes just the idea of getting tested for cancer scared them. They would start crying even before being tested."

But screening worked. The quality of screening by health workers was comparable to that of an expert gynecologist, researchers reported. The study was planned for 16 years, but results at 12 years showed lives were saved with the screening. So independent monitors advised offering it to the women in the comparison group.

An ethics controversy developed during the study. The U.S. Office for Human Research Protections faulted researchers for not adequately informing participants in the comparison group about Pap tests for screening. A letter from the agency in March indicated officials seemed to accept many of the remedies study leaders had implemented.

Others defended the study.

"We looked at the ethics very carefully" and felt them to be sound, and visited the project in India, said Trimble of the National Cancer Institute.

Dr. Sandra Swain, a cancer specialist at Medstar Washington Hospital Center, also defended the research. She is president of the American Society of Clinical Oncology, and the research results were presented at that group's meeting in Chicago on Sunday.

"There really was no wrongdoing there," she said. "They have no screening anyway," so there is no standard of care now.

Officials in India already are making plans to expand the vinegar testing to a wider population.

Many poor countries can't afford mammograms for breast cancer screening either. The India study also has been testing breast exams by health workers as an alternative. Preliminary results suggest breast cancers are being found at an earlier

stage, but it's too soon to know if that will save lives because not enough women have died yet to compare the groups, said Trimble of the National Cancer Institute.

More progress against cervical cancer may come from last month's announcement that two companies will drastically lower prices on HPV vaccines for poor countries. Pilot projects will begin in Asia and Africa; the campaign aims to vaccinate more than 30 million girls in more than 40 countries by 2020.

Associated Press Chief Medical Writer Marilynn Marchione reported from Chicago.

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: [CAS/CFAS-Mail] OHRP Puts Hold on SUPPORT-Related Compliance Actions; Other News
Date: Wednesday, June 05, 2013 10:09:36 AM

I got this one. If they are repetitive then no.thx.

Sent from my iPhone

On Jun 5, 2013, at 10:04 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Let me know if you want me to send all of these.
>
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> NIH
> 6100 Executive Blvd., Room 4B03
> MSC 7510
> Bethesda, MD 20892
> For overnight delivery use Rockville, MD 20852
> 301-435-7909
> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov
>
> **From:** Rowe, Mona (NIH/NICHD) [E]
> **Sent:** Wednesday, June 05, 2013 10:00 AM
> **To:** Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
> **Subject:** FW: [CAS/CFAS-Mail] OHRP Puts Hold on SUPPORT-Related Compliance Actions; Other News
>
> In case you didn't see from elsewhere –the emails and reports will start coming
>
> *Mona*
> Mona Jaffe Rowe, M.C.P.
> Associate Director for Science Policy,
> Analysis and Communication
> *Eunice Kennedy Shriver* National Institute of
> Child Health and Human Development
> National Institutes of Health, DHHS
> Building 31, Rm 2A-18
> 31 Center Drive

Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Burklow, John (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 9:54 AM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: Fwd: [CAS/CFAS-Mail] OHRP Puts Hold on SUPPORT-Related Compliance Actions; Other News

FYI

John Burklow
Associate Director for Communications and Public Liaison
National Institutes of Health
Building 1, Room 344
(301) 496-4461 (phone)
(301) 496-0017 (fax)
burklowj@od.nih.gov

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Celebration of Science at NIH: *watch how medical research saves lives and improves health*

Begin forwarded message:

> **From:** Tony Mazzaschi <tmazzaschi@aamc.org>
> **Date:** June 5, 2013, 9:47:35 AM EDT
> **To:** John Burklow <burklowj@od.nih.gov>
> **Subject: [CAS/CFAS-Mail] OHRP Puts Hold on SUPPORT-Related Compliance Actions; Other News**
> **Reply-To:** <tmazzaschi@aamc.org>
>
> The HHS Office of Human Research Protections (OHRP), citing strong disagreement by many with its earlier determination critical of the informed consent form in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT), has "put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further action involving similar designs until the process of producing appropriate guidance is completed." In taking the action, which appears to be unprecedented, OHRP acknowledged that "applying the 'reasonable foreseeable risk' concept to randomized studies of standard of care treatments is a complex undertaking." The Office said that it now recognizes its "obligation to provide clear guidance on what the rules are with regard to

disclosure of risks in randomized studies whose treatments fall within the range of standard of care." OHRP said it will develop such guidance in an open process.
http://tinyurl.com/OHRP-SUPPORT

In response to a call from the Obama administration to further the national dialogue on mental health, the AAMC and the American Psychological Association (APA) on Monday announced a collaboration to expand a free, online collection of mental health educational resources to equip health care professionals and medical students with the knowledge they need to improve mental health screenings and early identification of mental health concerns. The announcement was made the same day both organizations joined President Obama and Vice President Biden - along with mental health advocates, health care providers, faith leaders, government officials, educators, and individuals who have experienced mental health problems - for the National Conference on Mental Health that was convened at the White House.
http://tinyurl.com/mhn7k52

NIH on Monday posted a fact sheet on the impact of sequestration on the NIH. The summary includes a set of FAQs on the impact of the cuts on grantees. NIH reported that due to sequestration approximately 700 fewer competitive research project grants will be issued this fiscal year.
http://www.nih.gov/news/health/jun2013/nih-03.htm

Four leaders of Florida Atlantic University wrote a commentary in Wednesday's South Florida Sun Sentinel, stating that proposed cuts to the NIH budget would be devestating to research and to the patients researchers are trying to help. The four FAU authors were David J. Bjorkman, Dean and Executive Director of Medical Affairs, College of Medicine; Gary W. Perry, Dean, College of Science; Barry T. Rosson, Vice President for Research and Dean of the Graduate College; and Marlaine Smith, Dean, College of Nursing.
http://tinyurl.com/mdewo5z

The Pharmaceutical Research and Manufacturers of America (PhRMA) on Monday announced that Dr. William Chin will become Executive Vice President of Science and Regulatory Affairs, effective July 1. Dr. Chin is currently the Executive Dean for Research at Harvard Medical School. He rejoined Harvard from Lilly in 2010. At PhRMA, he will oversee the organization's scientific and regulatory affairs portfolio, including implementation of the Prescription Drug User Fee Act (PDUFA), clinical trials, and drug discovery and research collaboration, among other key issues. Dr. Chin is an internist and endocrinologist.
http://tinyurl.com/mnxzopg

E. Gordon Gee, president of The Ohio State University, and Robert H. Schottenstein, chairman of the OSU Board of Trustees,

announced on Tuesday that Dr. Gee plans to retire from the OSU presidency, effective July 1. Executive Vice President and Provost Joseph A. Alutto will be named interim president. Dr. Alutto, whose Ph.D. is in organizational behavior, previously served as interim president in 2007.
http://tinyurl.com/kx7mmyo

The New York Times on Monday reported that "Government officials, drug companies and medical experts, faced with outbreaks of antibiotic-resistant 'superbugs,' are pushing to speed up the approval of new antibiotics, a move that is raising safety concerns among some critics. The need for new antibiotics is so urgent, supporters of an overhaul say, that lengthy studies involving hundreds or thousands of patients should be waived in favor of directly testing such drugs in very sick patients. Influential lawmakers have said they are prepared to support legislation that allows for faster testing."
http://tinyurl.com/mjqx28j

The Boston Globe on Tuesday reported that Boston Medical Center "is considering closing a portion of its campus and eliminating 85 beds to address state and federal budget cuts and to shift more resources to outpatient services." Commenting on the story, one reader wrote "that this could be the first wave of such changes, as the days when 'health care was a sort of bomb shelter from the economy' may be ending."
http://tinyurl.com/kr3bn93

The National Institute of General Medical Sciences has posted a summary of the November workshop on "Research on Women in Biomedical Careers." The workshop focused on recent studies on causal factors and possible interventions affecting the representation of women in biomedical and behavioral research and engineering.
http://tinyurl.com/k6oucem

HHS on Monday announced that the Centers for Medicare & Medicaid Services (CMS) "released new data - including county-level data on Medicare spending and utilization for the first time, as well as selected data on hospital outpatient charges. In addition, the HHS Office of the National Coordinator for Health Information Technology (ONC) released additional information on the adoption of specific electronic health record (EHR) systems, as well as the winners of new opportunities for building innovative tools that build off health data."
http://www.dhhs.gov/news/press/2013pres/06/20130603b.html

The Episcopal Diocese of Texas on Friday announced that the sale of St. Luke's Episcopal Health System to Catholic Health Initiatives (CHI), the nation's third-largest faith-based health system, has been finalized. The transfer of the system, which now will be the St. Luke's Health System, includes the Texas Medical Center campus,

as well as suburban hospital locations in The Woodlands, Sugar Land, Pasadena and The Vintage. According to the announcement, "CHI will continue to grow and enhance St. Luke's significant affiliations with Baylor College of Medicine, Texas Heart Institute, Kelsey-Seybold Clinic, Texas Children's Hospital and MD Anderson Cancer Center."
http://tinyurl.com/kyacj8q

Wednesday's Federal Register contains a formal request from the Presidential Commission for the Study of Bioethical Issues for public comment "on the ethical, legal, and social issues raised by incidental findings that arise from genetic and genomic testing, imaging, and testing of biological specimens conducted in the clinical, research, and direct-to-consumer contexts." Comments are due by July 5.
http://www.gpo.gov/fdsys/pkg/FR-2013-06-05/html/2013-13329.htm

Media reports in Los Angeles and in Minnesota report, "The boards of the Hazelden Foundation and the Betty Ford Center -- two of the country's largest and most preeminent addiction treatment providers -- have engaged in talks of a possible 'alliance,' officials from both organizations announced Tuesday." A merger has not been ruled out. According to the Pioneer Press, Hazelden had $130 million in annual income and $211 million in net assets, according to its 2011 tax filing. The Betty Ford Center had about $40 million in annual income and $56 million in net assets.
http://tinyurl.com/m9re6xz

Monday's issue of The Oregonian, published in Portland, featured a profile of Dr. Shoukhrat Mitalipov, the OHSU researcher whose paper on SCNT was recently published by Cell.
http://tinyurl.com/mcbxd24

The Office of Management and Budget (OMB) last week issued new guidance to all federal agencies and employees concerning travel and conference expenses. The guidance was welcomed by many scientific societies as it states that federal agencies are encouraged to approve federal employee attendance at conferences that support agency missions.
http://tinyurl.com/lz7o6qq

Peter L. Elkin, MD, vice president and professor of medicine at the Mount Sinai School of Medicine and director of its Center for Biomedical Informatics, has been appointed professor and founding chair of the University at Buffalo's new Department of Biomedical Informatics.
http://tinyurl.com/lc87ay5

Our colleagues at Public Responsibility in Medicine & Research have announced the program and opened registration for the 2013 Advancing Ethical Research (AER) Conference. The meeting will be

held in Boston on November 7-9, with pre-conference programs on November 6. This is considered an essential meeting for those interested in learning the latest regulatory updates, strategies, and best practices in human subjects protections.
http://www.primr.org/aer13/

Jeanne M. Nerbonne, PhD, the Alumni Endowed Professor of Molecular Biology and Pharmacology, has been named director of the Center for Cardiovascular Research at the Washington University School of Medicine.
http://news.wustl.edu/news/Pages/25501.aspx

Dr. Sidney Wolfe, founder and longtime director of Public Citizen Health, has announced he is stepping down. He will be succeeded by Dr. Michael Carome, who has been deputy director. Dr. Carome, a nephrologist, was on the staff of the HHS Office for Human Research Protections before joining Public Citizen in 2010.
http://tinyurl.com/k7qg6nu

Tony Mazzaschi
AAMC

PS: Feel free to email <cas@aamc.org> if you have a problem accessing any article or resource mentioned in this summary. Also, have colleagues email <cas@aamc.org> if they would like to receive these news postings. We also welcome news tips and corrections.

PPS: Other news, policy, and innovation products from AAMC may be of particular interest to subscribers:
+AAMCAction, an iPhone, iPad and Android app featuring AAMC news and advocacy resources
https://www.aamc.org/advocacy/aamcaction/
+AAMC STAT (Short, Topical and Timely), a weekly news email highlights news related to academic medicine
http://www.aamc.org/newsroom/aamcstat/aamcnews.htm (note subscription box on right)
+AAMC Washington Highlights, a weekly summary of legislative & regulatory developments affecting academic medicine
http://www.aamc.org/advocacy/washhigh/subscribe.htm
+AAMC Second Opinion, news and perspectives from AAMC's Chief Public Policy Officer
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http://academicmedicineblog.org/ and its Twitter feed @AcadMedJournal

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial
Date: Wednesday, June 05, 2013 9:42:48 AM
Attachments: Wyckoff Authorship Levan.txt
B Stoll Authorship - J LeVan.pdf
Brion NICHD NRN Authorship Responsibility- LPB.pdf
Carlo Authorship Responsibility LeVan.pdf
Finer Authorship LeVan.txt
Gantz Authorship LeVan.tif
Heyne Authorship_Responsibility-signed_rjh.pdf
Jaleel Authorship Responsibility.pdf
levan.pdf
Sanchez NICHD NRN LeVan.pdf

Rose, Stephanie

I attach all the authors' authorship forms I have received.

I am missing 3 forms: Rose, Abhik and Lisa.

Best regards,

Luc

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luc.brion@utsouthwestern.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, May 28, 2013 9:50 AM
To: Luc Brion; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Yes – have them fill out the authorship forms prior to publications subcommittee review

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, May 28, 2013 10:49 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Rose:
I have sent the manuscript to all authors.
Should I send them the NRN Authorship document now or after Lisa and Marie have finalized the statistics?
Luc

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, May 28, 2013 7:37 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Luc Brion
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Have all the GDB co-authors seen and approved it?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, May 28, 2013 8:37 AM
To: 'Luc Brion'; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Rose,

Does Luc need to do anything else with Dr. LeVan's revised analysis plan other than work with Marie to complete it for the paper?

Stephanie

Stephanie Wilson Archer

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, May 23, 2013 10:26 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: revised protocol

Stephanie;
Please let me know what I need to do to get this going forward.
Thanks
Luc

Luc P. Brion, MD
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luc.brion@utsouthwestern.edu

From: Luc Brion
Sent: Wednesday, May 15, 2013 8:29 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: revised protocol

You are right; she did present a portion of what was planned in the protocol.
This is just a revision to match what was done so far and match what everyone has decided (Marie,

Wally, etc).

Luc

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From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Wednesday, May 15, 2013 8:20 AM
To: Luc Brion
Cc: Meg Cunningham (mcunningham@rti.org)
Subject: RE: revised protocol

Hi Luc,

I thought that Dr. LeVan presented her abstract at PAS this month. Can you tell me if her proposal is just a revision of what will be analyzed for the manuscript or a brand new PAS Abstract?

Thanks,

Stephanie

Stephanie Wilson Archer
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Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, May 13, 2013 10:29 PM
To: Archer, Stephanie (NIH/NICHD) [E]; 'mcunningham@rti.org'

Subject: Fw: revised protocol

For PAS 2014
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, May 13, 2013 06:18 PM
To: (b)(6) @gmail.com (b)(6) @gmail.com>; Wrage, Lisa Ann <wrage@rti.org>; Gantz, Marie <mgantz@rti.org>; Myra Wyckoff <Myra.Wyckoff@UTSouthwestern.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Roy Heyne <Roy.Heyne@UTSouthwestern.edu>; Mambarambath Jaleel <Mambarambath.Jaleel@UTSouthwestern.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Das, Abhik <adas@rti.org>; Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion <Luc.Brion@UTSouthwestern.edu>
Subject: revised protocol

Roy suggested to include the 2011 GDB information in the sample size calculation.
The number is almost identical to the 2010 GDB data.
Here is a revised version of the protocol including the 2011 data (page 11).
Best regards,
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
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NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

Title of manuscript: Changes in therapy and outcomes associated with the SUPPORT Trial
First author Jaclyn LeVan

☑ A. I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. I agree to allow the corresponding author to serve as the primary correspondent with the journal editorial office, to review the edited typescript and proof.

☑ B. I have read and given final approval of the submitted manuscript.

C. To qualify for authorship, you must check at least 1 box for each of the 3 categories of contributions listed below.

I have made substantial contributions to the intellectual content of the paper as described below.

1. (check at least 1 of the 3 below)

   ☐ conception and design
   ☑ acquisition of data
   ☐ analysis and interpretation of data

2. (check at least 1 of 2 below)

   ☐ drafting of the manuscript
   ☑ critical revision of the manuscript for important intellectual content

3. (check at least 1 below)

   ☐ statistical analysis
   ☑ obtaining funding
   ☑ administrative, technical, or material support
   ☐ supervision
   ☐ no additional contributions
   ☐ other (specify)
   ☐ or are disclosed in an attachment.

Your Signature Barbara J. Stoll Date Signed June 4, 2013

NICHD Neonatal Research Network

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Your Signature _____ Date Signed 5/28/2013

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First author __Jaclyn LeVan_____

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   ☐ supervision
   ☐ no additional contributions
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   ☐ or are disclosed in an attachment.

Your Signature Waldemar A. Carlo Date Signed 06-04-2013

Waldemar A. Carlo

Finer Authorship LeVan

From: Finer, Neil <nfiner@ucsd.edu>
Sent: Tuesday, June 04, 2013 2:16 PM
To: Luc Brion
Subject: RE: Alternative way to complete the Authorship Responsibility form for Jackie LeVan's paper

Here is my reply
Good luck Luc
Neil

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, June 04, 2013 8:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann; Myra Wyckoff; Pablo Sanchez; Finer, Neil;
Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Alternative way to complete the Authorship Responsibility form for Jackie LeVan's paper

Dear coauthors,
Please complete the authorship form below for Jackie LeVan's manuscript and return it to me. I
will collect them all and forward to Bill Truog. For reference, you can see how I listed your
contribution on page 2 of the manuscript (attached).
Let me know if I need to modify my description of your contributions.
Thanks,
Luc

NICHD Neonatal Research Network

Authorship Responsibility Form
(adapted from ICMJE and JAMA)

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below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C
and checking the appropriate boxes.

Title
Changes in therapy and outcomes associated with the SUPPORT Trial
Authors
Jaclyn M LeVan, DO, Luc P Brion, MD, Lisa Wrage, MPH, Marie Gantz, PhD,
Myra H Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD,
Mambarambath Jaleel, MD, Neil Finer, MD, Waldemar Carlo, MD,
Abhik Das, PhD, Barbara Stoll, MD, Rose Higgins, MD

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3. (check at least 1 below)

___ statistical analysis
___ obtaining funding
___ administrative, technical, or material support
___ supervision
___ no additional contributions
___ other (specify)
__X_ or are disclosed in an attachment.

Your Signature _____ Date Signed ___June 4 2013_____
(If sending from your email, you do not need to sign - that is acceptable as an "e-signature.)

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
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Finer Authorship LeVan

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Title of manuscript CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL
First author Jackie M. LeVan

☑ A. I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. I agree to allow the corresponding author to serve as the primary correspondent with the journal editorial office, to review the edited typescript and proof.

☑ B. I have read and given final approval of the submitted manuscript.

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   ☐ supervision
   ☑ no additional contributions
   ☐ other (specify)
   ☐ or are disclosed in an attachment.

Your Signature Roy Heyne MD Date Signed 5/28/2013

NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

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Title of manuscript CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL
First author JACLYN LEVAN

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Title of manuscript Changes in Therapy and Outcomes Associated with SUPPORT Trial
First author Jacqueline DeVani, DO

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Your Signature [signature] Date Signed 5/29/12

NICHD Neonatal Research Network

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First author __Jaclyn LeVan_____

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   ☐ supervision
   ☐ no additional contributions
   ☐ other (specify)
   ☐ or are disclosed in an attachment.

Your Signature Paula J Fuiman Date Signed 6/4/13

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: SUPPORT Update
Date: Wednesday, June 05, 2013 9:00:00 AM

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Burklow, John (NIH/OD) [E]
Sent: Wednesday, June 05, 2013 8:52 AM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT Update

Hi, Mona--I talked to Tait at HHS. We are going to field the calls as they come. Sometimes we'll refer to the statement--other times, we may want KH or FC to speak. HHS wants us just to refer to the article. That will not satisfy most reporters. We (Calvin, Renate, me) will be at HHS today for a meeting. We will discuss with ASPA folks. We will keep you in the loop.

John

John Burklow
Associate Director for Communications and Public Liaison
National Institutes of Health
Building 1, Room 344
(301) 496-4461 (phone)
(301) 496-0017 (fax)
burklowj@od.nih.gov

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On Jun 5, 2013, at 8:30 AM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

Hi Kathy- just reading this over again -- should we be prepared to send any calls

for comments or statements to the DHHS -- should we get a general statement ready here -- Rose and I spoke--we can work with Bob and Renate and get something together if you like

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, June 04, 2013 11:53 PM
To: Briggs, Josephine (NIH/NCCAM) [E]; Shurin, Susan (NIH/NHLBI) [E]; Gibbons, Gary (NIH/NHLBI) [E]; Maddox, Yvonne (NIH/NICHD) [E]; McGarey, Barbara (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Hann, Della (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: SUPPORT Update

Hello,

I wanted to provide an update on the SUPPORT study since quite a bit has happened over the last week and tomorrow will be a big day for SUPPORT.

First, HHS will announce at ~5 p.m. tomorrow (and then publish in the fed reg a few days later) a notice about an upcoming public meeting to discuss issues raised by the support controversy. The notice states that "HHS specifically is requesting input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process." A draft is attached. It has undergone changes since this version so this is for you to read and delete as final will arrive soon.

Second, OHRP has sent UAB a new letter that includes a statement that they will halt all compliance actions on support and studies with similar designs. That letter has been sent to uab and will be posted on ohrp webpage at 5 tomorrow. copy attached-

Third, an article, "In Support of SUPPORT - A View from the NIH," will appear at 5 pm tomorrow in early online version of NEJM. (draft attached - edits still in the works)

And finally, appearing in the same issue of NEJM will be a letter from a large group of bioethicists objecting to OHRP's action on SUPPORT. (final text attached though I understand there may be more signatories.)

Please don't share these documents (or, if you must share, share carefully) as some are being edited and we really want all of them to pop out at the same time late tomorrow.

Thanks for everything you have done and are doing to advance this important discussion. More to follow on how we wish to shape the public meeting.

Best,
kathy

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)
Date: Wednesday, June 05, 2013 8:02:09 AM

A step in the right direction

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 6:12 PM
To: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Buchanan, Lisa (HHS/OASH)
Sent: Tuesday, June 04, 2013 04:53 PM
To: marchase@uab.edu <marchase@uab.edu>
Cc: jonathanm@uab.edu <jonathanm@uab.edu>; furthalr@uab.edu <furthalr@uab.edu>; wsax@rti.org <wsax@rti.org>; jmc@rti.org <jmc@rti.org>; dborasky@rti.org <dborasky@rti.org>; amg@rti.org <amg@rti.org>; Hamburg, Margaret A. (FDA); Less, Joanne (FDA/OC); Mills, Sherry (NIH/OD) [E]; Ellis, Joe (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; rhm3@case.edu <rhm3@case.edu>; rhm3@case.edu <rhm3@case.edu>; jwagner@wfubmc.edu <jwagner@wfubmc.edu>; Thughes@wihri.org <Thughes@wihri.org>; clyde_briant@Brown.EDU <clyde_briant@Brown.EDU>; thomas.parks@neuro.utah.edu <thomas.parks@neuro.utah.edu>; jane.strasser@uc.edu <jane.strasser@uc.edu>; sblanchard1@tuftsmedicalcenter.org <sblanchard1@tuftsmedicalcenter.org>; angela.wishon@UTSouthwestern.edu <angela.wishon@UTSouthwestern.edu>; david.wynes@emory.edu <david.wynes@emory.edu>; gary_chadwick@urmc.rochester.edu <gary_chadwick@urmc.rochester.edu>; vpr@iu.edu <vpr@iu.edu>; NanLee@stanfordmed.org <NanLee@stanfordmed.org>; jbixby@med.miami.edu <jbixby@med.miami.edu>; hilary.ratner@wayne.edu <hilary.ratner@wayne.edu>; james-walker@uiowa.edu <james-walker@uiowa.edu>; andrew.rudczynski@yale.edu <andrew.rudczynski@yale.edu>; Firestein, Gary Steven; dan.gross@sharp.com <dan.gross@sharp.com>; proth@salud.unm.edu <proth@salud.unm.edu>
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Dear Dr. Marchase:

Attached is OHRP's letter regarding our evaluation of the SUPPORT trial. Please do not hesitate to contact me should you have any questions regarding this matter.

Thank you,

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
DHHS, Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Ph: 240-453-8298

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Confidential-Fw: SUPPORT Update
Date: Wednesday, June 05, 2013 5:38:47 AM
Attachments: SUPPORT town hall FR notice 5 31 13.doc
DCOI U Ala Birmingham 060413 signed .pdf
3huds_p1306986_OLF_NIHrev.pdf
Supportfinalwilfond.pdf

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, June 04, 2013 11:53 PM
To: Briggs, Josephine (NIH/NCCAM) [E]; Shurin, Susan (NIH/NHLBI) [E]; Gibbons, Gary (NIH/NHLBI) [E]; Maddox, Yvonne (NIH/NICHD) [E]; McGarey, Barbara (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Hann, Della (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
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Thanks for everything you have done and are doing to advance this important discussion. More to follow on how we wish to shape the public meeting.

Best,
kathy

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

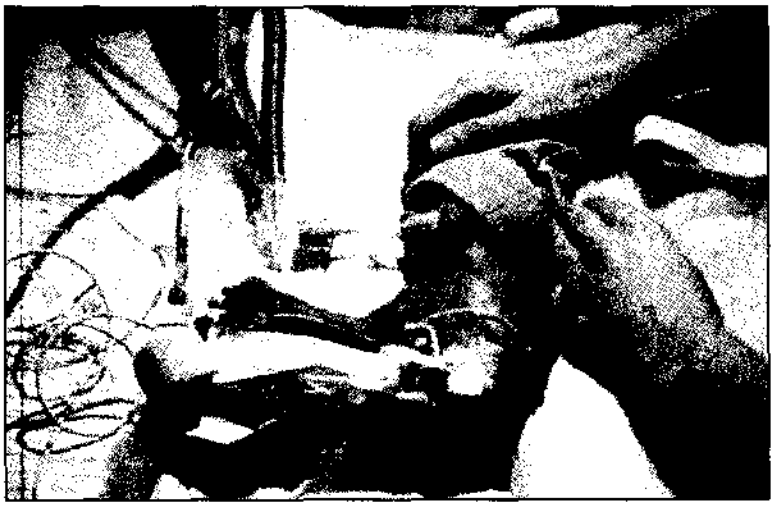
In Support of SUPPORT — A View from the NIH

Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

Each year in the United States, nearly 500,000 infants — 1 in every 8 — are born prematurely, before 37 weeks of gestation. Despite substantial advances in their care, premature infants face a daunting array of challenges; they are at high risk for death in infancy and face severe and lifelong health problems if they survive.[1] The National Institutes of Health (NIH) has a legal and moral responsibility to do research in partnership with scientists and families to optimize the care of these highly vulnerable infants. In recent weeks, a major public debate has arisen regarding a study designed to do just that. And the ramifications go well beyond this one study: the outcome of this debate could affect how we conduct and communicate about critical research on interventions that are within the standard of care for all diseases and conditions.

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), carried out at more than 20 sites between 2004 and 2009, sought to identify, in infants born very prematurely at 24 to 27 weeks' gestation, the oxygen-saturation level within the range considered the standard of care that would minimize the risk of retinopathy of prematurity (ROP), a complication of oxygen therapy that can result in vision loss.[2] When the study began, targeting an oxygen-saturation range of 85 to 95% was becoming standard clinical practice, and the American Academy of Pediatrics (AAP) later recommended this range in its 2007 guidelines. The SUPPORT researchers and institutional review boards (IRBs), practicing clinicians, and the AAP had no scientific evidence to expect a difference in mortality between the two treatment groups in SUPPORT — one with the oxygen saturation target of 85 to 89%, the other with the target of 91 to 95%.

An important finding of the study was a reduced incidence of ROP in the lower oxygen-saturation range. However, contrary to what was known at the time, the study also showed a slightly but significantly increased incidence of death — 19.9% versus 16.2% ($P=0.04$) — among infants assigned to the lower as compared with the upper range. As a result, last year the AAP amended its guidelines, citing SUPPORT, and physicians treating very premature infants are starting to use higher saturation rates to reduce the risk of death, even with the potentially higher risk of ROP at these levels. Studies such as SUPPORT that compare two alternatives, both within current standard clinical practice, often lead to critical improvements in medical care.



The federal Office for Human Research Protections (OHRP), which is charged with providing leadership in the protection of the rights, welfare, and well-being of persons involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS), asserted in March 2013, on the basis of their own examination of the evidence, that the SUPPORT researchers failed to provide prospective parents sufficient information about the risks posed by the study. After a detailed review of the protocol, the relevant consent documents, and the research literature, we respectfully disagree with the conclusions of OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPORT study commenced. Moreover, there is a larger issue here: how risks should be conveyed in the informed-consent process when research is comparing interventions that are all considered to be the standard of care.

In a letter dated March 7, 2013, the OHRP asserted that the study's consent form failed to convey that "the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death."[3] Their finding was influenced by research conducted in the 1950s, but in our view, it failed to assign proper weight to studies conducted in premature infants in the 2000s, which used more sophisticated oxygen-monitoring and -measurement devices, similar to those used in SUPPORT.[4] The more recent studies showed no increased risk of death or neurodevelopmental impairment at saturation levels as low as 70%.[5]

Given these data, the investigators had no reason to foresee that infants in one study group would have a higher risk of death than would those in the other group. The babies included in SUPPORT were, of course, facing substantial risks because of prematurity — the same risks as premature babies who were not enrolled in the study — but their care was never compromised for the sake of the study. The sample consent form for SUPPORT stated that each of the "possible combinations of treatments is considered by some units to represent their desired approach" (http://www.nih.gov/icd/od/foia/library/Records.htm). This statement describes the clinical equipoise at the time of the study, which was, in fact, the justification for conducting a clinical trial. Although the OHRP took issue with the consent form, it stated that the study design was ethical — a conclusion worth emphasizing. The increased risk of death was a significant and unexpected finding of the study; if it had been known before the study began, standard clinical care would not have encompassed the lower oxygen range, and it would have been unethical to conduct the study.

The NIH is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. We are strongly committed to supporting critical research studies like SUPPORT, which inform clinical care by providing rigorous evidence for use in daily practice. This controversy has alarmed some of the parents of infants who were in the study, confused the biomedical research community, and befuddled IRBs. Several other studies seeking new insights to improve care for these vulnerable infants have been put on hold as the field tries to understand the OHRP findings.

But controversies such as this are also an opportunity to advance shared understanding, provide clarification, and encourage

progress. The public debate surrounding the SUPPORT study has set the stage for a substantive national dialogue with the research, advocacy, and ethics communities on how best to respect and protect participants in research studies conducted within the standard of care and how to define "reasonably foreseeable risks" in this setting. The timing is critical — the clinical research community, bioethicists, regulators, IRBs, and prospective research participants are paying close attention now. The NIH is happy to work with all stakeholders to advance this important dialogue and its translation into clear guidance, in accordance with the plan being announced by the DHHS (*URL to come*). In addition, a letter from the OHRP to the University of Alabama at Birmingham is available now on the OHRP Web site (*URL may be forthcoming*).

Going forward, the NIH strongly and unequivocally supports the importance of the role of the OHRP in the oversight of human subjects research. But the community will benefit from an explicit description of the process the OHRP follows for investigating complaints. For example, when questions are raised about reasonably foreseeable risks and the state of the science relevant to a particular clinical trial, appropriate independent experts might need to be consulted. Finally, we are pleased to see the DHHS plan to ensure that investigators and IRBs will have a fair and transparent process for appealing OHRP findings and compliance actions, in those situations in which reasonable people disagree about the actions taken.

The SUPPORT study has unquestionably created controversy in the research community, but that circumstance now provides an opportunity for a better understanding of the scientific and ethical issues that must be addressed when designing such studies in the future. We look forward to working with OHRP, the research community, and patient advocates to improve the effectiveness and ethical standards of research involving human participants.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the National Institutes of Health, Bethesda, MD.

This article was published on June 5, 2013, at NEJM.org.

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DOI: 10.1056/NEJMp1306986

DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 4, 2013

Richard B. Marchase, Ph.D.
V.P. for Research & Economic Development
University of Alabama at Birmingham
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

Research Project:	The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
Principal Investigator:	Dr. Waldemar A. Carlo
HHS Protocol Number:	2U10HD034216

Dear Dr. Marchase:

In the wake of extensive scientific and public discussions since our March 7, 2013, determination letter in the SUPPORT study, OHRP has become aware of widespread misunderstanding about the risks that are required to be disclosed in obtaining informed consent for certain types of clinical trials. Our goal in this letter is to clarify several issues related to our determination.

At the outset, we wish to emphasize that OHRP does not and has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent, a bedrock principle of research involving human subjects.

To make truly informed decisions about whether or not to participate in a research study, potential volunteers or their parents or guardians are entitled to certain information, including a description of reasonably foreseeable risks. We acknowledge that the UAB consent form included language that reflected then-current research suggesting that lower saturation targets reduced the risk of retinopathy of prematurity (ROP), as well as language about the potential risks of ROP with prolonged use of supplemental oxygen. However, the "Risks" section of that form failed to mention and appropriately describe, as it should have, that relationship. More

significantly, neither the "Risks" section nor any other portion of the form mentioned any risks associated with lower oxygen levels.

OHRP recognizes that the SUPPORT investigators did not design the study with the expectation that they would find a difference in mortality rates between the high and low oxygen groups. Whereas much earlier studies of oxygen supplementation in premature babies had shown risks of mortality and neurological damage at very low oxygen levels, more recent studies did not demonstrate such risks. Consequently, when the SUPPORT study was initiated, there was no clear recent evidence indicating that different oxygenation levels within the then-current standard of care (85%-95%) would produce differences in neurological damage or survival.

However, the medical profession looks at many factors when assessing potential risks. At the outset of the SUPPORT study, many in the research and clinical communities remained concerned about the possible relationship between low oxygen and increased mortality and neurodevelopmental problems within the oxygen ranges that were to be evaluated in that study.[1] Indeed, such concerns were a core reason why the study was conducted. Those concerns were sufficient to affect clinical decisions and discouraged some doctors from treating premature infants at lower oxygen levels.

Indeed, descriptions of the process of designing the SUPPORT study and four similar studies conducted in other countries indicate a clear awareness of such concerns and the need to resolve them. This is evidenced by multiple statements from the SUPPORT investigators and other experts,[2] who identified the important need for a large randomized study with sufficient power to detect differences in mortality rates of 5% or greater.

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[1] See note 2, below.

[2] "In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct [what would become known as] the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration." Askie et al., BMC Pediatrics 2011 11:6, at page 3. That collaboration eventually included the SUPPORT study and four similar studies conducted within Canada (COT), the United Kingdom (BOOST-II UK), Australia (BOOST-II), and New Zealand (BOOST NZ). The initial thinking behind this group of studies was "outlined in a [2003] commentary in *Pediatrics*" in which Cole et al., Resolving Our Uncertainty About Oxygen Therapy, *Pediatrics* 2003;112:1415, discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." They also noted a particular challenge in recruiting neonatal units to participate: some units "regard [oxygen levels greater than 90%] as mandatory," and might therefore be unwilling to participate in a study in which one-half of the infants would be randomized to levels below 90%. To recruit such units, they suggested using "cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy."

Subsequent official statements regarding SUPPORT and the other four trials, issued prior to the 2010 results from SUPPORT, demonstrate that resolving those "real concerns" about mortality risks at the low oxygen end remained a major issue for these studies. On the official registration system for clinical trials in the U.S., clinicaltrials.gov, the SUPPORT researchers, in 2005, provided a one-sentence description, saying that it "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants." http://clinicaltrials.gov/archive/NCT00233324/2005_10_04 The description provided on that same database for the

Some commentators, in discussing the risks involved in the SUPPORT study, have attached great importance to the fact that all the oxygen levels to which the infants were assigned were within the range of the standard care.[3] But they draw inappropriate conclusions from that fact. Medicine is an imperfect science. When considerable uncertainty exists about the best way to treat a particular medical problem, the range of what can be considered standard care often is quite broad, to allow physicians to exercise clinical judgment on behalf of their patients.[4] Indeed, a core principle of medical ethics requires physicians to make such judgments, even in the face of uncertainty. All of us, as patients, rely on our doctors to do precisely that.

This principle has direct bearing on the SUPPORT study. When there is a range of oxygen levels within the standard of care, clinicians (and their institutions) often do, in fact, make their own determinations regarding which oxygen levels within that range to employ in treating their patients. Some physicians, recognizing the particular concerns about risks near the low (85%) and high (95%) ends of that range, might choose to avoid one or both of those regions.

The version of the consent form used at one SUPPORT site specifically acknowledged this to be the case; at that center, for clinical purposes, oxygen saturation was "kept between 88 and 94%."[5] Assuming the researchers achieved the distribution of oxygen levels they were trying to attain, research subjects at that site had a greater than 25% chance of being treated with an oxygen saturation between 85 and 88%, whereas, for those treated outside the study, the likelihood of being treated with oxygen in that range was quite small. Thus, by participating in

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Canadian trial in 2008 states that a randomized trial "is urgently needed and long overdue to determine whether oxygen exposure can be reduced safely in extremely preterm infants without increasing the risk of hypoxic death or disability." The United Kingdom protocol noted that "restricting oxygen exposure to minimize [the possibility of severe retinopathy] risks increasing early mortality." http://clinicaltrials.gov/archive/NCT00637169/2008_03_14 See also Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004 (113):394-396 ("For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP blindness, chronic lung disease, and brain damage) was, and remains to this day, unknown"); Tin et al, Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106–F110 ("Because mortality went undocumented in the first of the large trials of oxygen administration, we do not even know if there is a price to be paid for controlling administration strictly enough to minimise the risk of severe retinopathy.") . A Cochrane Collaboration review in 2009 specifically looked at the relationship between oxygen levels and mortality, concluding that the correct range to use was still not yet known. With regard to the most recent studies (from 2001 to 2004) showing no increased mortality at lower oxygen ranges, it noted: "these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide," and that the SUPPORT and other four studies were collecting data to "help resolve this remaining question." Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews 2009(1).

[3] Drazen JM, Solomon CG, Greene MF. Informed Consent and SUPPORT. N Engl J Med 2013;368:1929; Magnus D, Caplan AL. Risk, Consent and SUPPORT. N Engl J Med 2013;368:1864; Lantos JD. OHRP and Public Citizen are Wrong about Neonatal Research on Oxygen Therapy. Hastings Center Bioethics Forum, April 18, 2013;.

[4] Shepherd L. The SUPPORT Study and the Standard of Care. Hastings Center Bioethics Forum, May 17, 2013.

[5] SUPPORT consent form, Tufts Medical Center, available at http://www.citizen.org/documents/support-study-consent-form.pdf.

the study, the treatment of such subjects was substantially altered to make it much more likely that they would be within the range in which there were significant concerns about increased mortality.

And this circumstance is likely not unique to that site. As another of the consent forms noted, the "aim in many units is to keep oxygen saturations between 88 and 92%."[6] For institutions with those clinical care policies, participating in the study would have significantly increased the chance of an infant being assigned to oxygen levels at both the very low (85 to 88%) and the very high ends (92 to 95%), as opposed to the level they would have received, had they not been in the study.[7]

Unless, as is extraordinarily unlikely, an institution used for clinical purposes exactly the same randomization assignment procedure that was used in the SUPPORT trial, every child in the SUPPORT trial experienced some change in the likelihood of being assigned to the various oxygen levels. And as the above discussion demonstrates, for at least some of the children participating in the SUPPORT trial, the effect of such participation was to specifically increase their likelihood of being assigned to oxygen levels close to either end of the range of standard care – and thus to oxygen levels at which, as a clinical matter, they would not have been assigned by their individual physicians, had they not been in the study.

Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and those of researchers. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation. Our society relaxes that requirement because of the need to conduct research, the results of which are important to us all. As a modest but crucial trade-off in allowing researchers such flexibility, society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed. For some if not many of the subjects in the SUPPORT study, research participation increased the chance that they were treated at one or another end of the standard of care range. Given the requirement that subjects be apprised of "reasonably foreseeable risks," it would seem appropriate that the parents of the infants should have been informed of the real concerns within the medical community regarding those oxygen levels.[8]

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[6] SUPPORT consent form, Duke University Health System, available at http://www.citizen.org/documents/support-study-consent-form.pdf .

[7] Imagine, for example, an institution whose clinical standard allowed the full range of standard care to be used, with the pulse oximeter alarm set to go off at the levels of 85% and 95%, and with the goal of trying to keep the infant in the middle of that range (near 90%). Even under that scenario, by participating in the trial, the likelihood of the infant ending up in the more extreme values (85 to 87% or 93 to 95%) would, under some plausible assumptions, have nearly doubled.

[8] As noted above, the UAB consent form mentioned no risks with regard to the use of lower oxygen levels. In contrast, a 2005 version of the consent form used in the New Zealand BOOST study included this language: "Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . The aim of this study is to determine, *within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%)*, whether targeting the lower end of

OHRP recognizes that applying the "reasonably foreseeable risk" concept to randomized studies of standard of care treatments is a complex undertaking. We want to be clear, however, that it is not necessary to disclose all theoretical risks present at the outset of every study. Moreover, disclosure of a risk is unnecessary when study participation has no potential to increase or modify that risk compared to what would have happened had the subject not been in the study.

The facts regarding the SUPPORT study and what was known about the use of oxygen to treat premature infants also are complicated. Accordingly, we appreciate that there is justification for an incomplete understanding of how those rules might apply to this study. In addition, there are some who disagree with OHRP's analysis of how the regulations should apply to such studies. Indeed, some of the researchers involved in the SUPPORT study and others have argued that there was no need for researchers to have obtained any consent from parents before placing their children in this study.[9] This discussion takes place in the midst of a much broader discussion regarding a proposal from a distinguished group of scholars that is receiving prominent attention, which argues for completely eliminating the need for any consent in similar studies – a change that would involve a major reframing of the rules for protecting research subjects.[10]

These are crucially important issues, not just with regard to our ability to be able to conduct research with appropriate oversight, but also with regard to fundamental questions about the obligations owed by doctors to patients. Given their importance, we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic.

In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further

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this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability." (BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ) Had such language been in the UAB consent form, there would likely have been no OHRP finding with regard to non-disclosure of the risks relating to mortality and neurodevelopmental problems. And the NeOProM 2011 write-up, mentioned in note 2 above, using only pre-2005 references, describes the risks issue as follows: "There are two opposing concerns. Less inspired oxygen [under 90%] may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development. More inspired oxygen [greater than 90%] may increase severe [retinopathy] and chronic lung disease."

[9] Rich W et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. Pediatrics 2012;129:480; Whitney SN. The Python's Embrace: Clinical Research Regulation by Institutional Review Boards. Pediatrics 2012;129:576.

[10] Faden RR et al. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. Hastings Center Report Special Report 2013;43(1):S16.

action in studies involving similar designs until the process of producing appropriate guidance is completed.

OHRP's top priority remains that of protecting research participants. For this reason, we look forward to the forthcoming public discussion, and assuring that important research can proceed both with appropriate protection of subjects and without confusion about which risks must be disclosed.

We appreciate the continued commitment of your institutions to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI
Mr. David Borasky, Chair IRB#1, RTI
Ms. Angela Greene, Chair IRB#2, RTI
Dr. Juesta M. Caddell, Chair IRB#3, RTI
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
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Dr. Yvonne Maddox, Deputy Director, NICHD
Dr. Rosemary Higgins, Program Scientist, NICHD
Dr. Robert H. Miller, Case Western Reserve University
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Dr. Janice D. Wagner, Wake Forest University School of Medicine
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Dr. Jane Strasser, University of Cincinnati
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Ms. Angela Wishon, University of Texas Southwestern Medical Center

Dr. David Wynes, Emory University School of Medicine
Dr. Gary Chadwick, MPH, University of Rochester, School of Medicine and Dentistry
Dr. Jorge Jose, Indiana University School of Medicine
Ms. Nancy J. Lee, Stanford University School of Medicine
Dr. John L. Bixby, University of Miami, Miller School of Medicine
Dr. Hilary H. Ratner, Wayne State University
Dr. James C. Walker, University of Iowa
Dr. Andrew Rudczynski, Yale University School of Medicine
Dr. Gary S. Firestein, University of California, San Diego
Dr. Daniel L. Gross, Sharp Mary Birch Hospital for Women and Newborns
Dr. Paul B. Roth, University of New Mexico Health Sciences Center

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Treuman Katz Center
for Pediatric Bioethics

May 27, 2013

Jerry Meniko , M.D., J.D.
Director
O ce for Human Research Protec ons
Department of Health and Human Services
Suite 200
1101 Woo on Parkway
Rockville, MD 20852

Dear Dr Meniko ,

We are a group of scholars and leaders in bioethics and pediatrics with extensive experience in ethical and regulatory issues in pediatrics and human subjects research. We urge you to withdraw the O ce for Human Research Protec ons' (OHRP) no ca on that the ins tu ons involved with the Surfactant, Posi ve Pressure, Oxygena on Randomized Trial (SUPPORT) failed to meet regulatory informed consent requirements, in par cular regarding reasonably foreseeable risks of enrollment in the study. We believe this conclusion was a substan ve error and will have adverse implica ons for future research.

SUPPORT was undertaken, in part, because neonatologists lacked reliable scien c evidence as to which oxygen satura on levels were the safest and most e ec ve for extremely premature babies. The infants included in the study were randomly assigned to oxygen satura on targets that were consistent with standard clinical care at the par cipa ng institutions. OHRP's conclusion that the study's experimental evalua on of these otherwise rou nely used oxygen satura on levels exposed subjects to addi onal risk (above the risks of rou ne clinical treatment) is not supported by evidence.

Furthermore, OHRP's conclusion that the SUPPORT investigators violated federal regulations in failing to include speci c informa on elements in the parental permission documents regarding risks of the study interven ons is without substan ve merit and overreaches. Although we acknowledge that the permission documents could have been improved, we disagree that the randomize assignment to a high oxygen satura on level or a low oxygen satura on level imposed addi onal risks that the inves gators failed to disclose. There is nothing to indicate that the ins tu onal bodies responsible for reviewing the SUPPORT study failed to exercise appropriate care and judgment as to all the factors required by the Common Rule in approving the study. OHRP should not sanc on research ins tu ons simply because it disagrees with their assessment of the risks of research, but should do so only if it nds that an ins tu on has failed to meet the terms of its federal-wide assurance, such as in the manner in which its IRB is cons tuted or operates.

In the absence of a formal mechanism for appeal, we urge the OHRP to regard this expression of disagreement by signatories represen ng leaders in research ethics and

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pediatrics as an appropriate basis for OHRP to reconsider this decision. Allowing the decision to stand would be unfair to the inves gators and ins tu ons involved in SUPPORT. It would also set a precedent that will impede ongoing and future pa ent-centered outcomes studies. Such studies are crucial to advance medical prac ce, reduce risks, improve outcomes, and enhance cost e ec veness, par cularly in pediatrics.

The consent process for clinical research can no doubt be improved. The recent scru ny of SUPPORT highlights the challenges faced in clinical research. We believe that these challenges can best be addressed through open discussions among the full range of relevant stakeholders. We stand ready to par cipate in any such discussions to assist OHRP and the Department in their e orts to assure the highest standards of ethics in research.

Sincerely,

Benjamin Wilfond, MD, Professor of Pediatrics, University of Washington; Director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

David Magnus, PhD, Thomas A. Ra n Professor of Medicine and Biomedical Ethics and Professor of Pediatrics, Director, Center for Biomedical Ethics, Stanford University*

Armand Antommaria, MD, PhD, Associate Professor of Pediatrics, University of Cincinna ; Director, Ethics Center, Cincinnati Children's Hospital Medical Center*

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Chris Feudtner, MD, PhD, MA Associate Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania; Steven D. Handler Endowed Chair of Medical Ethics, Director Department of Medical Ethics, Children's Hospital of Philadelphia

Joseph J. Fins, MD, E. William Davis, Jr., MD Professor of Medical Ethics, Chief, Division of Medical Ethics, Professor of Medicine, Weill Medical College of Cornell University and Director of Medical Ethics, New York Presbyterian Hospital-Weill Cornell Medical Center

Norman Fost, MD, MPH, Professor, Pediatrics and Bioethics, University of Wisconsin School of Medicine and Public Health

D. Micah Hester, PhD, Chief, Division of Medical Humani es, University of Arkansas for Medical Sciences; Clinical Ethicist, Arkansas Children's Hospital

Steven Jo e, MD, MPH, Associate Professor of Pediatrics, Global Health and Social Medicine, Harvard Medical School; Hospital Ethicist, Dana-Farber Cancer Ins tute

Je rey Kahn, PhD, MPH, Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy, Deputy Director for Policy and Administra on, Johns Hopkins Berman Ins tute of Bioethics

Nancy E. Kass, ScD, Phoebe R. Berman Professor of Bioethics and Public Health, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Deputy Director for Public Health, Johns Hopkins Berman Ins tute of Bioethics

Eric Kodish MD, FJ O'Neill Professor and Chair, Department of Bioethics, Professor of Pediatrics, Lerner College of Medicine, Cleveland Clinic

John D. Lantos MD, Professor of Pediatrics, University of Missouri at Kansas City; Director, Children's Mercy Hospital Bioethics Center

Laurence McCullough , PhD, Dalton Tomlin Chair in Medical Ethics and Health Policy, Professor of Medicine and Medical Ethics; Associate Director for Educa on, Center for Medical Ethics and Health Policy, Baylor College of Medicine

William Meadow, MD PhD, Professor of Pediatrics, Co-Director of Neonatology, University of Chicago

Ross McKinney, Jr., MD, Professor of Pediatric Infec ous Diseases; Director, Trent Center for Bioethics, Humani es and History of Medicine, Duke University and School of Medicine

P. Pearl O'Rourke, MD, Director, Human Research A airs, Partners HealthCare

Kathleen E. Powderly, CNM, PhD, Director, John Conley Division of Medical Ethics and Humani es, SUNY Downstate Medical Center

Lainie Friedman Ross, MD, PhD, Carolyn and Ma hew Bucksbaum Professor of Clinical Ethics, Professor, Departments of Pediatrics, Medicine, and Surgery, Co-Director, Ins tute for Transla onal Medicine, Associate Director, MacLean Center for Clinical Medical Ethics, University of Chicago

Richard Sharp, PhD Director of Research Center for Ethics, Humani es and Spiritual Care, Cleveland Clinic

Sadath Sayeed, MD, JD, Assistant Professor of Pediatrics, Global Health and Social Medicine, Harvard Medical School, Sta Neonatologist, Boston Children's Hospital

Jeremy Sugarman, MD, MPH, MA, Harvey M. Meyerho Professor of Bioethics and Medicine, Deputy Director for Medicine, Johns Hopkins Berman Ins tute of Bioethics

Tom Tomlinson, PhD, Director, Center for Ethics and Humani es in the Life Sciences, College of Human Medicine, Michigan State University

Robert D. Truog, MD, Professor of Medical Ethics, Anesthesiology, & Pediatrics, Director of Clinical Ethics, Harvard Medical School; Senior Associate in Critical Care Medicine, Children's Hospital Boston

Yoram T. Unguru, MD, MS, MA, Division of Pediatric Hematology/Oncology, The Herman and Walter Samuelson Children's Hospital at Sinai; Johns Hopkins Berman Ins tute of Bioethics

Kathryn L. Weise, MD, MA, Program Director, Cleveland Fellowship in Advanced Bioethics, Department of Bioethics, Cleveland Clinic

David Woodrum, MD, Professor Emeritus, Neonatology, Dept of Pediatrics, University of Washington School of Medicine, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Ins tute

Stuart Youngner, MD, Professor of Psychiatry and Cogni ve Science, Susan E. Watson Professor of Bioethics, Chair, Department of Bioethics, Case Western Reserve University*

[**individuals who work at the same institutions where the SUPPORT study was conducted*]

cc: The Honorable Kathleen Sibelius, Secretary, Department of Health and Human Services (HHS)

The Honorable Howard K. Koh, Assistant Secretary for Health, HHS

Dr. Francis Collins, Director, Na onal Ins tutes of Health

Dr. Alan E. Gu macher, Director, Eunice Kennedy Shriver Na onal Ins tute of Child Health and Development

Dr. Christopher Aus n, Director, Na onal Center for Advancing Clinical and Transla onal Sciences

Dr Richard B. Marchase, Vice President, Research, University of Alabama at Birmingham

Dr Je rey R Botkin, Chair, Secretary's Advisory Commi ee on Human Research Protec ons

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: photo of ELBW
Date: Tuesday, June 04, 2013 9:47:44 PM

I will assume (b)(5)
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 07:46 PM
To: Spong, Catherine (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: RE: photo of ELBW

Very very great (b)(5) ☺

Mona

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Xoxoxo cathy

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Sent: Tuesday, June 04, 2013 05:36 PM
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Cc: Spong, Catherine (NIH/NICHD) [E]
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To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: photo of ELBW
Date: Tuesday, June 04, 2013 9:28:09 PM

Stephanie-
Thanks so much for being so responsive to mona today!!
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Rowe, Mona (NIH/NICHD) [E]
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Subject: Fw: photo of ELBW
Date: Tuesday, June 04, 2013 9:27:19 PM

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Stephanie really helped with this as I was on a plane - great to (b)(5) !!
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Subject: Re: photo of ELBW
Date: Tuesday, June 04, 2013 6:36:59 PM

This is fine!
I have to turn my electronics off though--
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

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Analysis and Communication

Eunice Kennedy Shriver National Institute of

Child Health and Human Development

National Institutes of Health, DHHS

Building 31, Rm 2A-18

31 Center Drive

Bethesda, MD 20892-2425

Phone: 301.496.1877/Fax: 301.496.0588

Email: rowem@mail.nih.gov

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 5:39 PM
To: Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: photo of ELBW
Importance: High

----- Original Message -----

From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]

Sent: Tuesday, June 04, 2013 05:36 PM

To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

Cc: Spong, Catherine (NIH/NICHD) [E]

Subject: photo of ELBW

Here are photos of a baby currently in our (b)(6) I'm attaching several so you can decide which you like best. Her GA at birth was 24+4 weeks; BW was 400 grams - she would have been eligible for SUPPORT. Pregnancy complicated by chronic hypertension and superimposed pre-eclampsia necessitating induction of labor despite extreme prematurity. She was intubated in DR and given surfactant. Not sure you want this for the article, but she is currently enrolled in the TOP (Transfusion of Prematures) trial.

Please let me know if you need anything else - call me by cell if anything comes up this evening. Mom is thrilled to be of help.

Best,

Brenda

Brenda Poindexter, MD, MS

Professor of Pediatrics

Section of Neonatal-Perinatal Medicine

Indiana University School of Medicine

317.274.4768 (office) (b)(6) (cell) (b)(6) (pager) bpoindex@iu.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Re: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)
Date: Tuesday, June 04, 2013 6:25:25 PM

Just got in when you did
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, June 04, 2013 06:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Assume you have seen this?!

-----Original Message-----
From: Caddell, Juesta M.
Sent: Tuesday, June 04, 2013 05:05 PM Eastern Standard Time
To: Story, G. Edward; Buchholtz, Chris; Gibbons, Patrick; Das, Abhik; Zaterka-Baxter, Kristin; Wallace, Dennis
Cc: Sax, E. Ward; Bachrach, Jamia; Visscher, Wendy A.
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

FYI

-----Original Message-----
From: Buchanan, Lisa (HHS/OASH) [mailto:Lisa.Buchanan@hhs.gov]
Sent: Tuesday, June 04, 2013 4:54 PM
To: marchase@uab.edu
Cc: jonathanm@uab.edu; furthalr@uab.edu; Sax, E. Ward; Caddell, Juesta M.; dborasky@rti.org; Greene, Angela M.; Hamburg, Margaret A. (FDA); Less, Joanne (FDA/OC); Mills, Sherry (NIH/OD) [E]; Ellis, Joe (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; rhm3@case.edu; rhm3@case.edu; jwagner@wfubmc.edu; Thughes@wihri.org; clyde_briant@Brown.EDU; thomas.parks@neuro.utah.edu; jane.strasser@uc.edu; sblanchard1@tuftsmedicalcenter.org; angela.wishon@UTSouthwestern.edu; david.wynes@emory.edu; gary_chadwick@urmc.rochester.edu; vpr@iu.edu; NanLee@stanfordmed.org; jbixby@med.miami.edu; hilary.ratner@wayne.edu; james-walker@uiowa.edu; andrew.rudczynski@yale.edu; gfirestein@ucsd.edu; dan.gross@sharp.com; proth@salud.unm.edu

Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Dear Dr. Marchase:

Attached is OHRP's letter regarding our evaluation of the SUPPORT trial. Please do not hesitate to contact me should you have any questions regarding this matter.

Thank you,

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
DHHS, Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Ph: 240-453-8298

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)
Date: Tuesday, June 04, 2013 6:22:38 PM
Attachments: DCOI U Ala Birmingham 060413 signed .pdf

Assume you have seen this?!

-----Original Message-----
From: Caddell, Juesta M.
Sent: Tuesday, June 04, 2013 05:05 PM Eastern Standard Time
To: Story, G. Edward; Buchholtz, Chris; Gibbons, Patrick; Das, Abhik; Zaterka-Baxter, Kristin; Wallace, Dennis
Cc: Sax, E. Ward; Bachrach, Jamia; Visscher, Wendy A.
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

FYI

-----Original Message-----
From: Buchanan, Lisa (HHS/OASH) [mailto:Lisa.Buchanan@hhs.gov]
Sent: Tuesday, June 04, 2013 4:54 PM
To: marchase@uab.edu
Cc: jonathanm@uab.edu; furthalr@uab.edu; Sax, E. Ward; Caddell, Juesta M.; dborasky@rti.org; Greene, Angela M.; Hamburg, Margaret A. (FDA); Less, Joanne (FDA/OC); Mills, Sherry (NIH/OD) [E]; Ellis, Joe (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; rhm3@case.edu; rhm3@case.edu; jwagner@wfubmc.edu; Thughes@wihri.org; clyde_briant@Brown.EDU; thomas.parks@neuro.utah.edu; jane.strasser@uc.edu; sblanchard1@tuftsmedicalcenter.org; angela.wishon@UTSouthwestern.edu; david.wynes@emory.edu; gary_chadwick@urmc.rochester.edu; vpr@iu.edu; NanLee@stanfordmed.org; jbixby@med.miami.edu; hilary.ratner@wayne.edu; james-walker@uiowa.edu; andrew.rudczynski@yale.edu; gfirestein@ucsd.edu; dan.gross@sharp.com; proth@salud.unm.edu

Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Dear Dr. Marchase:

Attached is OHRP's letter regarding our evaluation of the SUPPORT trial. Please do not hesitate to contact me should you have any questions regarding this matter.

Thank you,

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
DHHS, Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Ph: 240-453-8298

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
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FAX: 240-453-6909

June 4, 2013

Richard B. Marchase, Ph.D.
V.P. for Research & Economic Development
University of Alabama at Birmingham
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

Research Project:	The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
Principal Investigator:	Dr. Waldemar A. Carlo
HHS Protocol Number:	2U10HD034216

Dear Dr. Marchase:

In the wake of extensive scientific and public discussions since our March 7, 2013, determination letter in the SUPPORT study, OHRP has become aware of widespread misunderstanding about the risks that are required to be disclosed in obtaining informed consent for certain types of clinical trials. Our goal in this letter is to clarify several issues related to our determination.

At the outset, we wish to emphasize that OHRP does not and has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent, a bedrock principle of research involving human subjects.

To make truly informed decisions about whether or not to participate in a research study, potential volunteers or their parents or guardians are entitled to certain information, including a description of reasonably foreseeable risks. We acknowledge that the UAB consent form included language that reflected then-current research suggesting that lower saturation targets reduced the risk of retinopathy of prematurity (ROP), as well as language about the potential risks of ROP with prolonged use of supplemental oxygen. However, the "Risks" section of that form failed to mention and appropriately describe, as it should have, that relationship. More

significantly, neither the "Risks" section nor any other portion of the form mentioned any risks associated with lower oxygen levels.

OHRP recognizes that the SUPPORT investigators did not design the study with the expectation that they would find a difference in mortality rates between the high and low oxygen groups. Whereas much earlier studies of oxygen supplementation in premature babies had shown risks of mortality and neurological damage at very low oxygen levels, more recent studies did not demonstrate such risks. Consequently, when the SUPPORT study was initiated, there was no clear recent evidence indicating that different oxygenation levels within the then-current standard of care (85%-95%) would produce differences in neurological damage or survival.

However, the medical profession looks at many factors when assessing potential risks. At the outset of the SUPPORT study, many in the research and clinical communities remained concerned about the possible relationship between low oxygen and increased mortality and neurodevelopmental problems within the oxygen ranges that were to be evaluated in that study.[1] Indeed, such concerns were a core reason why the study was conducted. Those concerns were sufficient to affect clinical decisions and discouraged some doctors from treating premature infants at lower oxygen levels.

Indeed, descriptions of the process of designing the SUPPORT study and four similar studies conducted in other countries indicate a clear awareness of such concerns and the need to resolve them. This is evidenced by multiple statements from the SUPPORT investigators and other experts,[2] who identified the important need for a large randomized study with sufficient power to detect differences in mortality rates of 5% or greater.

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[1] See note 2, below.

[2] "In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct [what would become known as] the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration." Askie et al., BMC Pediatrics 2011 11:6, at page 3. That collaboration eventually included the SUPPORT study and four similar studies conducted within Canada (COT), the United Kingdom (BOOST-II UK), Australia (BOOST-II), and New Zealand (BOOST NZ). The initial thinking behind this group of studies was "outlined in a [2003] commentary in *Pediatrics*" in which Cole et al., Resolving Our Uncertainty About Oxygen Therapy, *Pediatrics* 2003;112:1415, discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." They also noted a particular challenge in recruiting neonatal units to participate: some units "regard [oxygen levels greater than 90%] as mandatory," and might therefore be unwilling to participate in a study in which one-half of the infants would be randomized to levels below 90%. To recruit such units, they suggested using "cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy."

Subsequent official statements regarding SUPPORT and the other four trials, issued prior to the 2010 results from SUPPORT, demonstrate that resolving those "real concerns" about mortality risks at the low oxygen end remained a major issue for these studies. On the official registration system for clinical trials in the U.S., clinicaltrials.gov, the SUPPORT researchers, in 2005, provided a one-sentence description, saying that it "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants." http://clinicaltrials.gov/archive/NCT00233324/2005_10_04 The description provided on that same database for the

Some commentators, in discussing the risks involved in the SUPPORT study, have attached great importance to the fact that all the oxygen levels to which the infants were assigned were within the range of the standard care.[3] But they draw inappropriate conclusions from that fact. Medicine is an imperfect science. When considerable uncertainty exists about the best way to treat a particular medical problem, the range of what can be considered standard care often is quite broad, to allow physicians to exercise clinical judgment on behalf of their patients.[4] Indeed, a core principle of medical ethics requires physicians to make such judgments, even in the face of uncertainty. All of us, as patients, rely on our doctors to do precisely that.

This principle has direct bearing on the SUPPORT study. When there is a range of oxygen levels within the standard of care, clinicians (and their institutions) often do, in fact, make their own determinations regarding which oxygen levels within that range to employ in treating their patients. Some physicians, recognizing the particular concerns about risks near the low (85%) and high (95%) ends of that range, might choose to avoid one or both of those regions.

The version of the consent form used at one SUPPORT site specifically acknowledged this to be the case; at that center, for clinical purposes, oxygen saturation was "kept between 88 and 94%."[5] Assuming the researchers achieved the distribution of oxygen levels they were trying to attain, research subjects at that site had a greater than 25% chance of being treated with an oxygen saturation between 85 and 88%, whereas, for those treated outside the study, the likelihood of being treated with oxygen in that range was quite small. Thus, by participating in

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Canadian trial in 2008 states that a randomized trial "is urgently needed and long overdue to determine whether oxygen exposure can be reduced safely in extremely preterm infants without increasing the risk of hypoxic death or disability." The United Kingdom protocol noted that "restricting oxygen exposure to minimize [the possibility of severe retinopathy] risks increasing early mortality." http://clinicaltrials.gov/archive/NCT00637169/2008_03_14 See also Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004 (113):394-396 ("For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP blindness, chronic lung disease, and brain damage) was, and remains to this day, unknown"); Tin et al, Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106–F110 ("Because mortality went undocumented in the first of the large trials of oxygen administration, we do not even know if there is a price to be paid for controlling administration strictly enough to minimise the risk of severe retinopathy.") . A Cochrane Collaboration review in 2009 specifically looked at the relationship between oxygen levels and mortality, concluding that the correct range to use was still not yet known. With regard to the most recent studies (from 2001 to 2004) showing no increased mortality at lower oxygen ranges, it noted: "these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide," and that the SUPPORT and other four studies were collecting data to "help resolve this remaining question." Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews 2009(1).

[3] Drazen JM, Solomon CG, Greene MF. Informed Consent and SUPPORT. N Engl J Med 2013;368:1929; Magnus D, Caplan AL. Risk, Consent and SUPPORT. N Engl J Med 2013;368:1864; Lantos JD. OHRP and Public Citizen are Wrong about Neonatal Research on Oxygen Therapy. Hastings Center Bioethics Forum, April 18, 2013;.

[4] Shepherd L. The SUPPORT Study and the Standard of Care. Hastings Center Bioethics Forum, May 17, 2013.

[5] SUPPORT consent form, Tufts Medical Center, available at http://www.citizen.org/documents/support-study-consent-form.pdf.

the study, the treatment of such subjects was substantially altered to make it much more likely that they would be within the range in which there were significant concerns about increased mortality.

And this circumstance is likely not unique to that site. As another of the consent forms noted, the "aim in many units is to keep oxygen saturations between 88 and 92%."[6] For institutions with those clinical care policies, participating in the study would have significantly increased the chance of an infant being assigned to oxygen levels at both the very low (85 to 88%) and the very high ends (92 to 95%), as opposed to the level they would have received, had they not been in the study.[7]

Unless, as is extraordinarily unlikely, an institution used for clinical purposes exactly the same randomization assignment procedure that was used in the SUPPORT trial, every child in the SUPPORT trial experienced some change in the likelihood of being assigned to the various oxygen levels. And as the above discussion demonstrates, for at least some of the children participating in the SUPPORT trial, the effect of such participation was to specifically increase their likelihood of being assigned to oxygen levels close to either end of the range of standard care – and thus to oxygen levels at which, as a clinical matter, they would not have been assigned by their individual physicians, had they not been in the study.

Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and those of researchers. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation: Our society relaxes that requirement because of the need to conduct research, the results of which are important to us all. As a modest but crucial trade-off in allowing researchers such flexibility, society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed. For some if not many of the subjects in the SUPPORT study, research participation increased the chance that they were treated at one or another end of the standard of care range. Given the requirement that subjects be apprised of "reasonably foreseeable risks," it would seem appropriate that the parents of the infants should have been informed of the real concerns within the medical community regarding those oxygen levels.[8]

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[6] SUPPORT consent form, Duke University Health System, available at http://www.citizen.org/documents/support-study-consent-form.pdf .

[7] Imagine, for example, an institution whose clinical standard allowed the full range of standard care to be used, with the pulse oximeter alarm set to go off at the levels of 85% and 95%, and with the goal of trying to keep the infant in the middle of that range (near 90%). Even under that scenario, by participating in the trial, the likelihood of the infant ending up in the more extreme values (85 to 87% or 93 to 95%) would, under some plausible assumptions, have nearly doubled.

[8] As noted above, the UAB consent form mentioned no risks with regard to the use of lower oxygen levels. In contrast, a 2005 version of the consent form used in the New Zealand BOOST study included this language: "Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . . The aim of this study is to determine, *within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%)*, whether targeting the lower end of

OHRP recognizes that applying the "reasonably foreseeable risk" concept to randomized studies of standard of care treatments is a complex undertaking. We want to be clear, however, that it is not necessary to disclose all theoretical risks present at the outset of every study. Moreover, disclosure of a risk is unnecessary when study participation has no potential to increase or modify that risk compared to what would have happened had the subject not been in the study.

The facts regarding the SUPPORT study and what was known about the use of oxygen to treat premature infants also are complicated. Accordingly, we appreciate that there is justification for an incomplete understanding of how those rules might apply to this study. In addition, there are some who disagree with OHRP's analysis of how the regulations should apply to such studies. Indeed, some of the researchers involved in the SUPPORT study and others have argued that there was no need for researchers to have obtained any consent from parents before placing their children in this study.[9] This discussion takes place in the midst of a much broader discussion regarding a proposal from a distinguished group of scholars that is receiving prominent attention, which argues for completely eliminating the need for any consent in similar studies – a change that would involve a major reframing of the rules for protecting research subjects.[10]

These are crucially important issues, not just with regard to our ability to be able to conduct research with appropriate oversight, but also with regard to fundamental questions about the obligations owed by doctors to patients. Given their importance, we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic.

In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further

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this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability." (BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ) Had such language been in the UAB consent form, there would likely have been no OHRP finding with regard to non-disclosure of the risks relating to mortality and neurodevelopmental problems. And the NeOProM 2011 write-up, mentioned in note 2 above, using only pre-2005 references, describes the risks issue as follows: "There are two opposing concerns. Less inspired oxygen [under 90%] may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development. More inspired oxygen [greater than 90%] may increase severe [retinopathy] and chronic lung disease."

[9] Rich W et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. Pediatrics 2012;129:480; Whitney SN. The Python's Embrace: Clinical Research Regulation by Institutional Review Boards. Pediatrics 2012;129:576.

[10] Faden RR et al. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. Hastings Center Report Special Report 2013;43(1):S16.

action in studies involving similar designs until the process of producing appropriate guidance is completed.

OHRP's top priority remains that of protecting research participants. For this reason, we look forward to the forthcoming public discussion, and assuring that important research can proceed both with appropriate protection of subjects and without confusion about which risks must be disclosed.

We appreciate the continued commitment of your institutions to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI
Mr. David Borasky, Chair IRB#1, RTI
Ms. Angela Greene, Chair IRB#2, RTI
Dr. Juesta M. Caddell, Chair IRB#3, RTI
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Dr. Yvonne Maddox, Deputy Director, NICHD
Dr. Rosemary Higgins, Program Scientist, NICHD
Dr. Robert H. Miller, Case Western Reserve University
Dr. Nancy C. Andrews, Duke University
Dr. Janice D. Wagner, Wake Forest University School of Medicine
Mr. Thomas Hughes, Women and Infants Hospital of Rhode Island
Dr. Clyde L. Briant, Brown University
Dr. Thomas N. Parks, University of Utah, School of Medicine
Dr. Jane Strasser, University of Cincinnati
Ms. Susan Blanchard, BBA, Tufts Medical Center
Ms. Angela Wishon, University of Texas Southwestern Medical Center

Dr. David Wynes, Emory University School of Medicine
Dr. Gary Chadwick, MPH, University of Rochester, School of Medicine and Dentistry
Dr. Jorge Jose, Indiana University School of Medicine
Ms. Nancy J. Lee, Stanford University School of Medicine
Dr. John L. Bixby, University of Miami, Miller School of Medicine
Dr. Hilary H. Ratner, Wayne State University
Dr. James C. Walker, University of Iowa
Dr. Andrew Rudczynski, Yale University School of Medicine
Dr. Gary S. Firestein, University of California, San Diego
Dr. Daniel L. Gross, Sharp Mary Birch Hospital for Women and Newborns
Dr. Paul B. Roth, University of New Mexico Health Sciences Center

From: Poindexter, Brenda B
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Abbot Laptook (alaptook@WIHRI.org); Abhik Das (adas@rti.org); Barbara Stoll (barbara_stoll@oz.ped.emory.edu); Brenda Poindexter (bpoindex@iupui.edu); Ed Bell (edward-bell@uiowa.edu); Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu); Krisa P. Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Michele C. Walsh (mcw3@cwru.edu); "Walsh, Michele" (Michele.Walsh@UHhospitals.org); Pablo Sanchez (Pablo.Sanchez@UTSouthwestern.edu); Richard Ehrenkranz (richard.ehrenkranz@yale.edu); Roger G. Faix (roger.faix@hsc.utah.edu); Ron Goldberg (goldb008@mc.duke.edu); Seetha Shankaran (sshankar@med.wayne.edu); Wally Carlo (wcarlo@peds.uab.edu); Mike Cotten (cotte010@mc.duke.edu); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Picture of a preemie
Date: Tuesday, June 04, 2013 6:00:11 PM

Haha...red....but Meg will attest it's DOTS when the candy bowl comes around!

Sent from my iPhone

On Jun 4, 2013, at 5:55 PM, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov> wrote:

> Brenda wins the prize! Thanks so much! Do you like red or white, milk or dark?
>
> _____
> From: Archer, Stephanie (NIH/NICHD) [E]
> Sent: Tuesday, June 04, 2013 4:54 PM
> To: 'Abbot Laptook (alaptook@WIHRI.org)'; Abhik Das (adas@rti.org); 'Barbara Stoll (barbara_stoll@oz.ped.emory.edu)'; 'Brenda Poindexter (bpoindex@iupui.edu)'; 'Ed Bell (edward-bell@uiowa.edu)'; 'Kathleen Kennedy (Kathleen.A.Kennedy@uth.tmc.edu)'; 'Krisa P. Van Meurs (vanmeurs@stanford.edu)'; 'Kristi Watterberg (kwatterberg@salud.unm.edu)'; 'Kurt Schibler (kurt.schibler@cchmc.org)'; 'Michele C. Walsh (mcw3@cwru.edu)'; 'Walsh, Michele' (Michele.Walsh@UHhospitals.org); 'Pablo Sanchez (Pablo.Sanchez@UTSouthwestern.edu)'; 'Richard Ehrenkranz (richard.ehrenkranz@yale.edu)'; 'Roger G. Faix (roger.faix@hsc.utah.edu)'; 'Ron Goldberg (goldb008@mc.duke.edu)'; 'Seetha Shankaran (sshankar@med.wayne.edu)'; 'Wally Carlo (wcarlo@peds.uab.edu)'; Mike Cotten (cotte010@mc.duke.edu); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org)
> Cc: Higgins, Rosemary (NIH/NICHD) [E]
> Subject: Picture of a preemie
>
> Hi Everyone,
>
> I've called or left messages for a few of you. We are hoping to have something about SUPPORT in NEJM tomorrow (to be kept confidential, of course!). They want a high-quality picture of a preemie who did or would have qualified for SUPPORT (one that is the right GA, etc. and on CPAP or intubated).
>
> Since this would be public, we would need the parent's permission to use the picture (anonymously), so I'm guessing it would be easier to see if you have such a baby currently in the NICU for a picture. The NEJM Photo Release consent form is here: http://www.nejm.org/userimages/ContentEditor/1274822530041/patientid.pdf.
>
> The kicker, of course, if that we need it TONIGHT!
>
> Please, if you have such a picture or can get it, give me a call on my cell phone at (b)(6)
>
> Thanks,
>
> Stephanie

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: photo of ELBW
Date: Tuesday, June 04, 2013 5:48:25 PM

Brenda
With heartfelt thanks!!!
Rose
Rosemary D. Higgins, MD
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From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 5:45 PM
To: 'Poindexter, Brenda B'
Cc: Archer, Stephanie (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: photo of ELBW

Thanks so much -- you are a miracle worker in many ways -- our very best to both mother and baby. We hope all goes well.

Mona
Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
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Phone: 301.496.1877/Fax: 301.496.0588
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-----Original Message-----
From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]
Sent: Tuesday, June 04, 2013 5:43 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: photo of ELBW

Importance: High

Mona,
I meant to also copy you on this email; Stephanie Archer asked me to send this.
Brenda

-----Original Message-----
From: Poindexter, Brenda B
Sent: Tuesday, June 04, 2013 5:36 PM
To: 'Archer, Stephanie (NIH/NICHD) [E]'; Rosemary Higgins (higginsr@mail.nih.gov)
Cc: 'spongc@dir49.nichd.nih.gov'
Subject: photo of ELBW
Importance: High

Here are photos of a baby currently in our (b)(6) - I'm attaching several so you can decide which you like best. Her GA at birth was 24+4 weeks; BW was 400 grams - she would have been eligible for SUPPORT. Pregnancy complicated by chronic hypertension and superimposed pre-eclampsia necessitating induction of labor despite extreme prematurity. She was intubated in DR and given surfactant. Not sure you want this for the article, but she is currently enrolled in the TOP (Transfusion of Prematures) trial.
Please let me know if you need anything else - call me by cell if anything comes up this evening. Mom is thrilled to be of help.
Best,
Brenda

Brenda Poindexter, MD, MS
Professor of Pediatrics
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Indiana University School of Medicine
317.274.4768 (office) | (b)(6) (cell) | (b)(6) (pager) bpoindex@iu.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: photo of ELBW
Date: Tuesday, June 04, 2013 5:48:00 PM

I think the one marked JPG 38 is the best
Rosemary D. Higgins, MD
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From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 5:40 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: photo of ELBW

These are wonderful Stephanie --you are a miracle worker along with the doctors and nurses who are caring for the baby

Mona
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-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 5:39 PM
To: Spong, Catherine (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: photo of ELBW
Importance: High

----- Original Message -----
From: Poindexter, Brenda B [mailto:bpoindex@iu.edu]
Sent: Tuesday, June 04, 2013 05:36 PM
To: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: photo of ELBW

Here are photos of a baby currently in our (b)(6) - I'm attaching several so you can decide which you like best. Her GA at birth was 24+4 weeks; BW was 400 grams - she would have been eligible for SUPPORT. Pregnancy complicated by chronic hypertension and superimposed pre-eclampsia necessitating induction of labor despite extreme prematurity. She was intubated in DR and given surfactant. Not sure you want this for the article, but she is currently enrolled in the TOP (Transfusion of Prematures) trial.
Please let me know if you need anything else - call me by cell if anything comes up this evening. Mom is thrilled to be of help.
Best,
Brenda

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Blansfield, Earl (NIH/NICHD) [E]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Tuesday, June 04, 2013 5:46 PM
To: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]
Subject: pdf from NEJM
Attachments: _3huds_p1306986_OLF_NIHrev.pdf

Hi everyone –

NEJM sent Kathy the pdf proof for review. I've marked it up in three places (attached). I've asked them to modify the text about the HHS statement and OHRP new letter as Francis revised it this afternoon – you'll see that as a bubble on the pdf. Also Debbie at NEJM asked me to double check the two quotes that we have in the text. I have done that and noted that they are both correct in bubbles.

Please check this and be sure everything else looks ok.

Finally, NEJM wanted a photo with a caption and the NICHD staff who provided the photo don't have specs on it anymore. I believe Mona and Rose (Alan, correct me if you know differently) were going to try to find another comparable photo of a premature infant within the age range of the SUPPORT Study.

Thoughts?

Steph

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Withheld pursuant to exemption

(b)(4),(b)(5)

of the Freedom of Information and Privacy Act

Page 0981 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5)

of the Freedom of Information and Privacy Act

From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann; Myra Wyckoff; Pablo Sanchez; Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Alternative way to complete the Authorship Responsibility form for Jackie LeVan"s paper
Date: Tuesday, June 04, 2013 2:53:38 PM
Attachments: Jackie LeVanManuscript NRN clean 06-3-13.doc

Dear coauthors,
Please complete the authorship form below for Jackie LeVan's manuscript and return it to me. I will collect them all and forward to Bill Truog. For reference, you can see how I listed your contribution on page 2 of the manuscript (attached).
Let me know if I need to modify my description of your contributions.
Thanks,
Luc

NICHD Neonatal Research Network

Authorship Responsibility Form
(adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

Title	Changes in therapy and outcomes associated with the SUPPORT Trial
Authors	Jaclyn M LeVan, DO, Luc P Brion, MD, Lisa Wrage, MPH, Marie Gantz, PhD, Myra H Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD, Mambarambath Jaleel, MD, Neil Finer, MD, Waldemar Carlo, MD, Abhik Das, PhD, Barbara Stoll, MD, Rose Higgins, MD

___ A. I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. I agree to allow the corresponding author to serve as the primary correspondent with the journal editorial office, to review the edited typescript and proof.

___B. I have given final approval of the submitted manuscript.

To qualify for authorship, you must check at least 1 box for each of the 3 categories of contributions listed below.

I have made substantial contributions to the intellectual content of the paper as described below.

1. (check at least 1 of the 3 below)

___ conception and design
___ acquisition of data
___ analysis and interpretation of data

2. (check at least 1 of 2 below)

___ drafting of the manuscript
___ critical revision of the manuscript for important intellectual content

3. (check at least 1 below)

___ statistical analysis
___ obtaining funding
___ administrative, technical, or material support
___ supervision
___ no additional contributions
___ other (specify)
___ or are disclosed in an attachment.

Your Signature _____ Date Signed _____
(If sending from your email, you do not need to sign – that is acceptable as an "e-signature.)

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UT Southwestern Medical Center
The future of medicine, today.

CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Changes associated with SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD SUPPORT trial showed that continuous positive airway pressure is an alternative to endotracheal intubation for delivery room therapy in very preterm infants.

What This Study Adds: The proportion of endotracheal intubation significantly decreased after the SUPPORT trial in NICHD centers that participated in the SUPPORT

Revised 5/28/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 231 words
Article length: 2,221 words

Abstract

Introduction
In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare care process and outcomes before SUPPORT and after its publication.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one. The proportion of DR intubation decreased only in centers with >=80% DR intubation prior to SUPPORT.

Discussion:
This study is limited by its observational before/after design.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within one hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in May 2010. The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of the current study was to determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of preterm inborn

infants intubated in the DR. We hypothesized that publication of SUPPORT would be followed by a decrease in proportion of intubation in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We hypothesized that the decrease in proportion of intubation in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. We also aimed to determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks, including risk of death or BPD (defined by oxygen use at 36 weeks of postmenstrual age (PMA)), death or severe ROP (defined as ROP surgery or retinal detachment) at the time of discharge and death before discharge. We also hypothesized that publication of SUPPORT would not affect the risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP (defined as ROP surgery or retinal detachment), and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those in the SUPPORT trial. Eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate, without known malformations, delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. We included patients who died early, but excluded patients whose support was either withheld or withdrawn.

Baseline variables

Neonatal and maternal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were intubation in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Secondary outcome variables:

Secondary outcomes of interest included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain

differences in means and 95% CI. These models included pre-specified prenatal covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted tests, and that preceded the outcome. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes. We created a model specific for BPD, considering the following potential covariates: intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch. Additionally, Chi Square tests were used to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations $\geq$ 80% (based on pre-SUPPORT proportion at Parkland, an NRN center which did not participate in the Feasibility Trial)[17] and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR intubation and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2). Secondary outcomes are shown in Tables 3 and 4. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of

life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the delivery room during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.18). Centers were also combined into two groups: two centers with pre-SUPPORT percent DR intubations < 80% and nine centers with pre-SUPPORT percent DR intubations ≥ 80%. The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks gestational age born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR intubation and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR intubation decreased significantly only in centers with

a high baseline proportion. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,[18] and between 2003 and 2007.[19] They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.[20] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes. The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in

severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] Delivery room practice, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[29]

Conclusion

After adjustment for baseline variables, the risk of DR intubation, ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT results. The adjusted risk of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after SUPPORT. These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

References

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3]	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second epoch.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

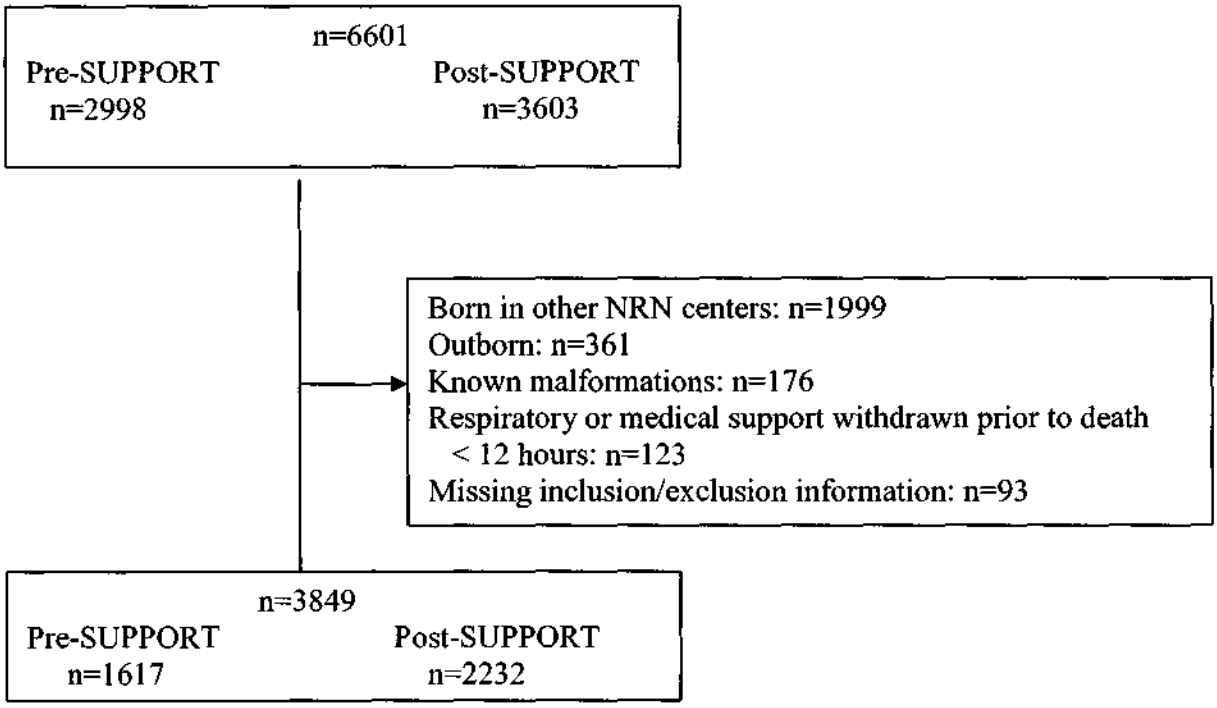
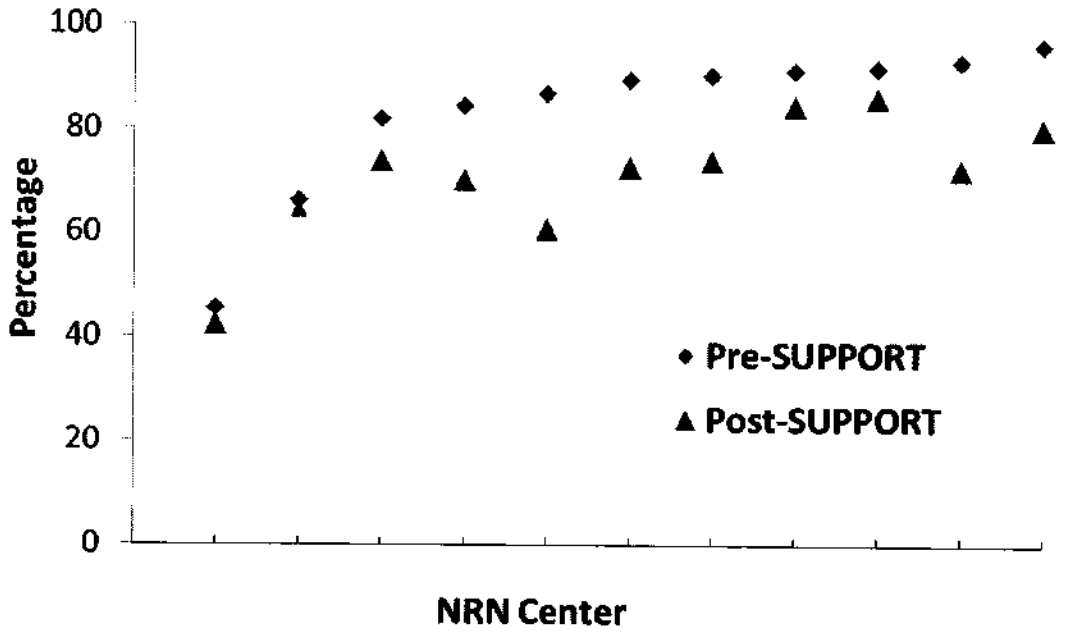


Figure 2



From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: Re: Edited NEJM Perspective article
Date: Tuesday, June 04, 2013 2:44:59 PM

I think christina stiles provided it
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Tuesday, June 04, 2013 02:38 PM
To: Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: Re: Edited NEJM Perspective article

Hi Mona and Rose,

The NEJM editor is asking again for a caption or credit to the photo you shared with us. I'm unclear on what that should be. Do you have guidance for us? We need to finalize this today - posting will be tomorrow.

Thank you!
Steph

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, May 28, 2013 11:53 AM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Edited NEJM Perspective article

There is no caption or credit –it has been in our files for a very long time (perhaps the baby is now in high school or college...)

Rose "certified" that of the neonate pictures we have – this one most likely looks like one who be of early gestational age (perhaps of the age that could have been enrolled in one of the NRN trials)

Mona

Mona Jaffe Rowe, M.C.P.
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From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 28, 2013 10:35 AM
To: Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Fwd: Edited NEJM Perspective article

Is there a caption or credit for preemie photo?

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

> **From:** "Malina, Debbie" <dmalina@nejm.org>
> **Date:** May 28, 2013, 9:28:31 AM EDT
> **To:** "'Hudson, Kathy (NIH/OD) [E]'" <Kathy.Hudson@nih.gov>
> **Subject: RE: Edited NEJM Perspective article**
>
> Hi, Kathy. The decision is to use the photo, so if there is a credit or anything, let me know. We are going to move the piece forward as is, just so we have it ready, but you can revise or rewrite the last couple of paragraphs when you receive the page proofs.
> Thanks.
> Debbie

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, May 27, 2013 5:11 PM
To: Malina, Debbie
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Edited NEJM Perspective article

Debbie,
Here are FC and AG edits along with a photo for you to consider.

FC and I have a call with senior hhs folks late tomorrow so too late for us to make online pub this week. Can we lock in publication for june 5? We are committed to that as last possible date.

We may need to tweak last two paragraphs a bit but will try to keep edits to minimum.

kathy

From: Hudson, Kathy (NIH/OD) [E]

Sent: Monday, May 27, 2013 11:55 AM
To: 'Malina, Debbie'
Subject: RE: Edited NEJM Perspective article

Thanks Debbie!
I just went through it and it looks good. Thanks for the nice edits. I sent it off to Alan and FC for their blessing and will have it back in your inbox later today.

From: Malina, Debbie [mailto:dmalina@nejm.org]
Sent: Monday, May 27, 2013 10:41 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Edited NEJM Perspective article

Dear Kathy,

I have edited your manuscript and am attaching the result for your review, revisions, and responses. Although I've saved a copy with my changes tracked, in case we need to check your original wording, this version has the edits tentatively accepted, for ease of reading. There are a few queries embedded in it as "comments"; if you can't locate these, please let me know.

I will have my assistant upload all the versions into our Manuscript Central system tomorrow, but in the meantime, you should probably just e-mail any new version directly to me so that we can keep this moving forward. I know we're waiting to hear about publication time, but just in case it's OK to go ahead on Wednesday, it would be great to have an officially accepted version ready to send to Production.

Thanks.

Best,
Debbie Malina

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From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Sunday, May 26, 2013 3:37 PM

To: Drazen, M.D., Jeff; Malina, Debbie
Cc: Morrissey, Stephen; Curfman, M.D., Gregory D.; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Draft of essay for NEJM on SUPPORT

Jeff/Debbie,
HHS is okay with the article but before it appears the Secretary wants to have a sense of what steps she will take in response to our "path ahead" conclusion. Francis and I are meeting with the Dep Sec and others in HHS on Tuesday and will offer our suggestions for how HHS might frame their response/next steps.

While the outcome of that meeting may be a green light for OHRP to send uab letter and for us to publish, I am nervous about committing to Wednesday online publication with things in such flux. That said, I think it is fantastic that we may be able shape some real reforms at OHRP. How much flexibility do you guys have on pub timing? Should I go ahead and submit manuscript now or wait?

Best,
Kathy

From: Drazen, M.D., Jeff [mailto:jdrazen@nejm.org]
Sent: Thursday, May 23, 2013 9:59 PM
To: Hudson, Kathy (NIH/OD) [E]; Morrissey, Stephen; Curfman, M.D., Gregory D.; Malina, Debbie
Subject: Re: Draft of essay for NEJM on SUPPORT

Kathy,
As soon as this is "cleared" please submit it on our web site (www.nejm.org) and send Debbie Malina (e-mail above) and me a copy by e-mail. It is close enough that Debbie can help you finish it off! We will try to post next Wednesday.
Best,
j

On 5/23/13 3:38 PM, "Kathy Hudson" <Kathy.Hudson@nih.gov> wrote:

We have sent this to hhs for "review" and expect comments back tomorrow but I wanted to share this version with you.

Jeffrey M. Drazen, M.D.
Editor-in-Chief, New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine, Harvard Medical School

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This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

From: Luc Brion
To: Wally Carlo, M.D.; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Myra Wyckoff; Pablo Sanchez; Finer, Neil
Cc: (b)(6)@gmail.com; Gantz, Marie; Mambarambath Jaleel; Barbara Stoll; Roy Heyne; Luc Brion
Subject: Authorship responsibility form for Jackie LeVan"s paper - REMINDER
Date: Tuesday, June 04, 2013 2:38:13 PM
Attachments: Authorship Responsibility LeVan.pdf
Jackie LeVanManuscript NRN 052813 LPB edlw4June13 changes (3).doc
Jackie LeVanManuscript NRN clean 06-3-13.doc

Wally, Lisa, Rose, Abhik, Myra, Pablo, Neil:

I attach the most recent version of the manuscript (one with the tracking and one clean with further minor typographical edits), in which all previous comments have been incorporated. If you have any comments or suggestions please let me know.

Could you please complete and sign the attached document and send it back to me by Friday.

Thanks

Luc

Luc P. Brion, MD
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UT Southwestern Medical Center
The future of medicine, today.

NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

Title of manuscript: Changes in therapy and outcomes associated with the SUPPORT Trial
First author __Jaclyn LeVan_____

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   ☐ statistical analysis
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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

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Short title: Changes associated with SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD SUPPORT trial showed that continuous positive airway pressure is an alternative to endotracheal intubation for delivery room therapy in very preterm infants.

What This Study Adds: The proportion of endotracheal intubation significantly decreased after the SUPPORT trial in NICHD centers that participated in the SUPPORT

Revised 5/28/13

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
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Abstract length: 231 words
Article length: 2,214 words

Abstract

Introduction
In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare care process and outcomes before SUPPORT and after its publication.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one. The proportion of DR intubation decreased only in centers with >=80% DR intubation prior to SUPPORT.

Discussion:
This study is limited by its observational before/after design.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ weeks to $27^{6/7}$ weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within one hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in May 2010. The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of the current study was to determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of preterm inborn

infants intubated in the DR. We hypothesized that publication of SUPPORT would be followed by a decrease in proportion of intubation in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We hypothesized that the decrease in proportion of intubation in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. We also aimed to determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks, including risk of death or BPD (defined by oxygen use at 36 weeks of postmenstrual age (PMA)), death or severe ROP (defined as ROP surgery or retinal detachment) at the time of discharge and death before discharge. We also hypothesized that publication of SUPPORT would not affect the risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP (defined as ROP surgery or retinal detachment), and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those in the SUPPORT trial. Eligible infants were inborn at $24^{0/7}$ to $27^{6/7}$ weeks at birth by best obstetrical estimate, without known malformations, delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. We included patients who died early, but excluded patients whose support was either withheld or withdrawn.

Baseline variables

Neonatal and maternal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were intubation in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before

discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Secondary outcome variables:

Secondary outcomes of interest included BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for apgar scores and skewed continous variables, ~~and~~ Student t-tests ~~or Wilcoxon tests, as appropriate,~~ for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. These models included pre-specified prenatal covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted tests, and that

preceded the outcome. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes. We created a model specific for BPD, considering the following potential covariates: intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch. Additionally, ~~the Cochran-Mantel-Haenszel~~ Chi Square tests were~~was~~ used to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations $\geq$ 80% (based on pre-SUPPORT proportion at Parkland, an NRN center which did not participate in the Feasibility Trial)[17] and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

Results

A total of 6,601 infants $24^{0/7}$ to $27^{6/7}$ weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an

additional 361 were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.0001), maternal hypertension (27.4% vs. 19.9%, p<0.0001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR intubation and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2).

Secondary outcomes are shown in Tables 3 and 4. The adjusted risks of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risks of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. Average ventilator days among survivors decreased by 4.7

days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the delivery room during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.187). Centers were also combined into two groups: two centers with pre-SUPPORT percent DR intubations < 80% and nine centers with pre-SUPPORT percent DR intubations ≥ 80%. The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks gestational age born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR intubation and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR intubation decreased significantly only in centers with a high baseline proportion. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96

and 1997-2002,[18] and between 2003 and 2007,[19] ~~(Stoll et al added reference to the list #19).~~ They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011,[20] ~~(Patel PAS abstract WILL SEND YOU THE DRAFT PAPER).~~ These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

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The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population and secular trends. Since this study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are

related to changes in median or ranges of oxygen saturation. ~~WOULD ADD THAT WE ALSO CONNOT determine the potential effect of changing O2 sat standards on overall ELBW mortality. This is a limitation of this study.~~ Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,[21] treatment and prophylaxis of patent ductus arteriosus,[22-24] synchronized nasal intermittent positive-pressure ventilation,[25] prevention of central line-associated bloodstream infections,[26,27] or nutrition.[28] Delivery room practice, including oxygen exposure and thermoregulation ~~and administration of epinephrine,~~ may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association,[29,27]

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Conclusion

After adjustment for baseline variables, the risks of DR intubation, ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT results. The adjusted risks of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risks of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after SUPPORT. -These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
(Maternal ??)Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adj p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	~~0.90 (0.84-~~ 0033
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<.0001

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[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

The pvalue for death or mechanical ventilation is .0033, it was not in the cell and the cell would not allow it to be entered for unknown reason so I deleted and added a cell, that's why this looks weird.

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication[3] ~~epinephrine **~~	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	~~4.4 (2.5)~~4 (2-6)	~~3.9 (2.4)~~4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<.0001
Apgar score, 5 min., median (IQR)	~~6.5 (2.0)~~7 (6-8)	~~6.3 (2.2)~~7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	.0025
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	1~~4~~3 (0.~~9~~8)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure ~~or nasal intermittent positive pressure ventilation~~ (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

[1] presented as ~~mean (SD),~~ mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge~~,~~ and length of hospital stay; **median (interquartile range) for apgar scores;** mean (SD) for all other continuous variables, and n (%) for categorical variables.

[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

[3] The definition of medications administered in the delivery room was limited to epinephrine for the second epoch.

[4] survivors to discharge or 120 days, whichever came first, max is 120 days.

~~**Lisa needs to take a closer look at this definition before finalized~~

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Figure 1

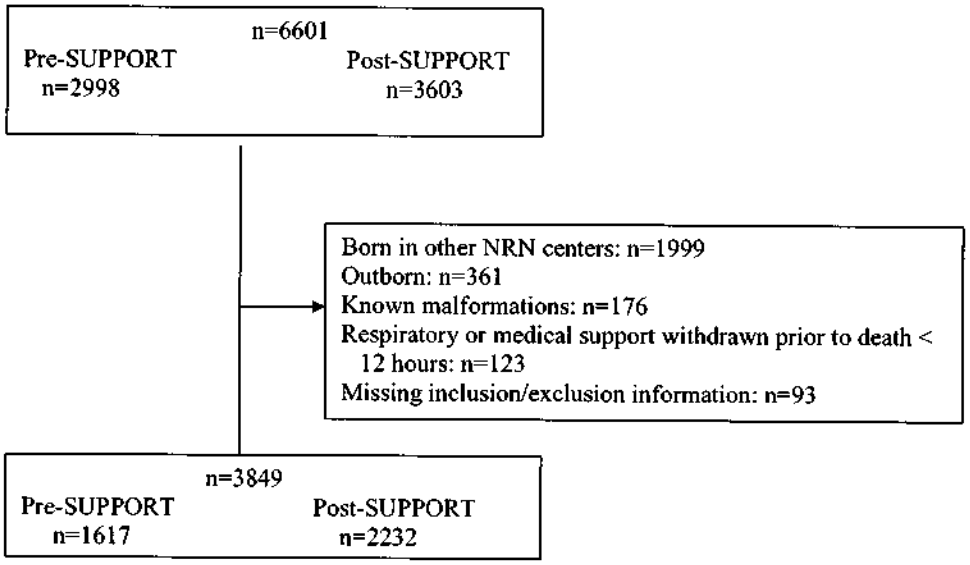
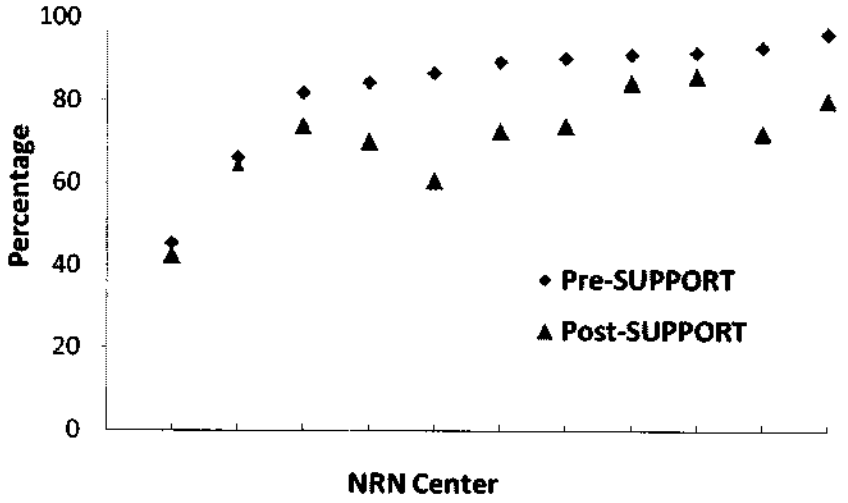


Figure 2



Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, June 04, 2013 2:14 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: NICHD NRN DSMC Model Consent Review

See below-

Thanks for all your help

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 04, 2013 01:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: NICHD NRN DSMC Model Consent Review

Hi Rose,

After review of the 6 active trial model consents, the DSMC has several recommendations primarily across all consents but some protocol specific items as well. No recommendations to drastically alter or stop any study based on consent elements so all studies can move forward as planned. Minutes will be drafted and sent to the DSMC for input, then to the Network per usual practice.

Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
Clinical Research Specialist
Social Policy, Health, & Economic Research
RTI International
3040 Cornwallis Rd
Research Triangle Park, NC 27709
Phone: 919-485-7750
Fax: 919-485-7762

From: Wally Carlo, M.D.
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: RE: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)
Date: Tuesday, June 04, 2013 11:22:25 PM

Yes, I got it. It is disappointing how government officials can be so misinformed and libelous. This is totally unacceptable behavior.

Wally

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, June 04, 2013 5:20 PM
To: Rosemary Higgins; Wally Carlo, M.D.; Finer, Neil
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Assume you have seen this?!

-----Original Message-----
From: Caddell, Juesta M.
Sent: Tuesday, June 04, 2013 05:05 PM Eastern Standard Time
To: Story, G. Edward; Buchholtz, Chris; Gibbons, Patrick; Das, Abhik; Zaterka-Baxter, Kristin; Wallace, Dennis
Cc: Sax, E. Ward; Bachrach, Jamia; Visscher, Wendy A.
Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

FYI

-----Original Message-----
From: Buchanan, Lisa (HHS/OASH) [mailto:Lisa.Buchanan@hhs.gov]
Sent: Tuesday, June 04, 2013 4:54 PM
To: marchase@uab.edu
Cc: jonathanm@uab.edu; furthalr@uab.edu; Sax, E. Ward; Caddell, Juesta M.; dborasky@rti.org; Greene, Angela M.; Hamburg, Margaret A. (FDA); Less, Joanne (FDA/OC); Mills, Sherry (NIH/OD) [E]; Ellis, Joe (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; rhm3@case.edu; rhm3@case.edu; jwagner@wfubmc.edu; Thughes@wihri.org; clyde_briant@Brown.EDU; thomas.parks@neuro.utah.edu; jane.strasser@uc.edu; sblanchard1@tuftsmedicalcenter.org; angela.wishon@UTSouthwestern.edu; david.wynes@emory.edu; gary_chadwick@urmc.rochester.edu; vpr@iu.edu; NanLee@stanfordmed.org; jbixby@med.miami.edu; hilary.ratner@wayne.edu; james-walker@uiowa.edu; andrew.rudczynski@yale.edu; gfirestein@ucsd.edu; dan.gross@sharp.com; proth@salud.unm.edu

Subject: FW: DCOI U Ala Birmingham 060413 signed--Scanned document from Borror, Kristina C (HHS/OASH) (Kristina.Borror@hhs.gov)

Dear Dr. Marchase:

Attached is OHRP's letter regarding our evaluation of the SUPPORT trial. Please do not hesitate to contact me should you have any questions regarding this matter.

Thank you,

Lisa Buchanan, MAOM
Public Health Analyst
Division of Compliance Oversight
DHHS, Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Ph: 240-453-8298

Blansfield, Earl (NIH/NICHD) [E]

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, June 03, 2013 10:01 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: NIH comments on docs for SUPPORT
Attachments: NEJM SUPPORT_060313_Final ogc.docx

Importance: High

Please see OGC comments within.

FC

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 03, 2013 7:29 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Schultz, William B (HHS/OGC); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Subject: RE: NIH comments on docs for SUPPORT
Importance: High

Francis,

(b)(5)

Thanks,

Caya

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]
Sent: Monday, June 03, 2013 6:13 PM
To: Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: NIH comments on docs for SUPPORT

Hi everyone,

Thanks to Caya for summarizing the status of the FRN. NIH is willing to go with the majority view on Sections IIB and III, though we urge that flexibility be maintained as much as possible in establishing the ultimate agenda for the public meeting.

We very much appreciate the edits on the UAB letter provided by Howard Koh earlier today.

Attached is a revised version of the NEJM essay, taking into consideration the thoughtful comments received from Bill Corr and Howard Koh. Given the tight deadline for NEJM, this version is being submitted to the editor this evening. It is almost certain that the editor will make some stylistic/grammatical/clarifying changes (editors of NEJM are famous for that), but this should be pretty close.

It will be great to get this all launched on Wednesday! Thanks to all of our HHS colleagues for the hard work it has taken to get us here.

Francis

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 03, 2013 4:26 PM
To: Schultz, William B (HHS/OGC); Corr, Bill (HHS/IOS); Koh, Howard (HHS/OASH); LaPan, Jarel (HHS/IOS); Menikoff, Jerry (HHS/OASH); Collins, Francis (NIH/OD) [E]; Dotzel, Peggy (HHS/OGC); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS)
Subject: RE: Draft FR Notice regarding Support Study
Importance: High

All,

It is (b)(5) today. Considering the comments from OHRP and NIH and those of Andrea, Bill and myself here I think there are two key issues left to resolve:

(b)(5)

Thank you,

Caya

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of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

Page 1049 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Blansfield, Earl (NIH/NICHD) [E]

From: Wilfond, Benjamin <benjamin.wilfond@seattlechildrens.org>
Sent: Friday, May 31, 2013 11:48 PM
To: Menikoff, Jerry (HHS/OASH)
Cc: Sebelius, Kathleen (HHS/OS); Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Austin, Christopher (NIH/NCATS) [E]; Hudson, Kathy (NIH/OD) [E]; Jeff Botkin; 'David Magnus'
Subject: Bioethics letter about suppport
Attachments: Supportfinalwilfond.pdf

Dear Dr Menikoff,

Attached is letter written by colleagues in bioethics and pediatrics about the OHRP finding about the SUPPORT Study. A version of this letter has been accepted for publication in the New England Journal of Medicine this week but we wanted to bring this to your direct attention.

This rationale for this letter was discussed at the Association of Bioethics Program Directors meeting in April and David Magnus and I decided to contact others in the field. We all agreed that the OHRP finding was overreaching. The scientific, clinical, and ethical issues are very complex, and none in our group believed that the concerns crossed the threshold of non compliance with the regulations. We are concerned about the implications of the finding for future research. We believe that when the issues are complex and there are a range of views on both sides, that engaged conversation with experts and the public are a better way to consider the concerns raised.

We urge you to withdraw this notification and welcome the opportunity to join you in further dialog about these issues.

Benjamin Wilfond MD
Director | Treuman Katz Center for Pediatric Bioethics
Seattle Children's Research Institute

Professor | Department of Pediatrics
University of Washington School of Medicine

206.884-8055 OFFICE
(b)(6) PAGER
206.[illegible] DIRECT
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MAIL M/S C9S-6 , 1900 Ninth Ave. Seattle, WA 98101
WWW seattlechildrens.org/bioethics

UW Medicine
SCHOOL OF MEDICINE

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Treuman Katz Center
for Pediatric Bioethics

May 27, 2013

Jerry Meniko , M.D., J.D.
Director
O ce for Human Research Protec ons
Department of Health and Human Services
Suite 200
1101 Woo on Parkway
Rockville, MD 20852

Dear Dr Meniko ,

We are a group of scholars and leaders in bioethics and pediatrics with extensive experience in ethical and regulatory issues in pediatrics and human subjects research. We urge you to withdraw the O ce for Human Research Protec ons' (OHRP) no ca on that the ins tu ons involved with the Surfactant, Posi ve Pressure, Oxygena on Randomized Trial (SUPPORT) failed to meet regulatory informed consent requirements, in par cular regarding reasonably foreseeable risks of enrollment in the study. We believe this conclusion was a substan ve error and will have adverse implica ons for future research.

SUPPORT was undertaken, in part, because neonatologists lacked reliable scien c evidence as to which oxygen satura on levels were the safest and most e ec ve for extremely premature babies. The infants included in the study were randomly assigned to oxygen satura on targets that were consistent with standard clinical care at the par cipa ng institutions. OHRP's conclusion that the study's experimental evalua on of these otherwise rou nely used oxygen satura on levels exposed subjects to addi onal risk (above the risks of rou ne clinical treatment) is not supported by evidence.

Furthermore, OHRP's conclusion that the SUPPORT investigators violated federal regulations in failing to include speci c informa on elements in the parental permission documents regarding risks of the study interven ons is without substan ve merit and overreaches. Although we acknowledge that the permission documents could have been improved, we disagree that the randomize assignment to a high oxygen satura on level or a low oxygen satura on level imposed addi onal risks that the inves gators failed to disclose. There is nothing to indicate that the ins tu onal bodies responsible for reviewing the SUPPORT study failed to exercise appropriate care and judgment as to all the factors required by the Common Rule in approving the study. OHRP should not sanc on research ins tu ons simply because it disagrees with their assessment of the risks of research, but should do so only if it nds that an ins tu on has failed to meet the terms of its federal-wide assurance, such as in the manner in which its IRB is cons tuted or operates.

In the absence of a formal mechanism for appeal, we urge the OHRP to regard this expression of disagreement by signatories represen ng leaders in research ethics and

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Seattle, WA 98101

bioethics.seattlechildrens.org

pediatrics as an appropriate basis for OHRP to reconsider this decision. Allowing the decision to stand would be unfair to the inves gators and ins tu ons involved in SUPPORT. It would also set a precedent that will impede ongoing and future pa ent-centered outcomes studies. Such studies are crucial to advance medical prac ce, reduce risks, improve outcomes, and enhance cost e ec veness, par cularly in pediatrics.

The consent process for clinical research can no doubt be improved. The recent scru ny of SUPPORT highlights the challenges faced in clinical research. We believe that these challenges can best be addressed through open discussions among the full range of relevant stakeholders. We stand ready to par cipate in any such discussions to assist OHRP and the Department in their e orts to assure the highest standards of ethics in research.

Sincerely,

Benjamin Wilfond, MD, Professor of Pediatrics, University of Washington; Director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

David Magnus, PhD, Thomas A. Ra n Professor of Medicine and Biomedical Ethics and Professor of Pediatrics, Director, Center for Biomedical Ethics, Stanford University*

Armand Antommaria, MD, PhD, Associate Professor of Pediatrics, University of Cincinna ; Director, Ethics Center, Cincinnati Children's Hospital Medical Center*

Paul Appelbaum, MD, Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law, Columbia University

Wylie Burke, MD, PhD, Professor and Chair, Department of Bioethics and Humani es, University of Washington School of Medicine

Renee D. Boss, MD, MHS, Division of Neonatology, Department of Pediatrics, Johns Hopkins School of Medicine; Johns Hopkins Berman Ins tute of Bioethics

Arthur L. Caplan, PhD, Drs. William F. and Virginia Connolly Mi y Chair, Director, Division of Medical Ethics, New York University Langone Medical Center

Alexander M. Capron, JD, University Professor, Sco H. Bice Chair in Healthcare Law, Policy and Ethics, Co-Director, Paci c Center for Health Policy and Ethics, University of Southern California

Ellen Wright Clayton, MD, JD, Professor of Law, Vanderbilt Law School; Craig-Weaver Professor of Pediatrics, Vanderbilt University School of Medicine

Mildred Cho, PhD, Professor of Pediatrics, Stanford University; Associate Director, Stanford Center for Biomedical Ethics, Stanford University*

Douglas Diekema, MD MPH, Professor of Pediatrics, University of Washington; Director of Education, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

Joel Frader MD MA, Professor of Pediatrics and Medical Humani es & Bioethics, Northwestern University

Ruth R. Faden, PhD, MPH, Philip Franklin Wagley Professor of Biomedical Ethics; Director, Johns Hopkins Berman Ins tute of Bioethics

Chris Feudtner, MD, PhD, MA Associate Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania; Steven D. Handler Endowed Chair of Medical Ethics, Director Department of Medical Ethics, Children's Hospital of Philadelphia

Joseph J. Fins, MD, E. William Davis, Jr., MD Professor of Medical Ethics, Chief, Division of Medical Ethics, Professor of Medicine, Weill Medical College of Cornell University and Director of Medical Ethics, New York Presbyterian Hospital-Weill Cornell Medical Center

Norman Fost, MD, MPH, Professor, Pediatrics and Bioethics, University of Wisconsin School of Medicine and Public Health

D. Micah Hester, PhD, Chief, Division of Medical Humani es, University of Arkansas for Medical Sciences; Clinical Ethicist, Arkansas Children's Hospital

Steven Jo e, MD, MPH, Associate Professor of Pediatrics, Global Health and Social Medicine, Harvard Medical School; Hospital Ethicist, Dana-Farber Cancer Ins tute

Je rey Kahn, PhD, MPH, Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy, Deputy Director for Policy and Administra on, Johns Hopkins Berman Ins tute of Bioethics

Nancy E. Kass, ScD, Phoebe R. Berman Professor of Bioethics and Public Health, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Deputy Director for Public Health, Johns Hopkins Berman Ins tute of Bioethics

Eric Kodish MD, FJ O'Neill Professor and Chair, Department of Bioethics, Professor of Pediatrics, Lerner College of Medicine, Cleveland Clinic

John D. Lantos MD, Professor of Pediatrics, University of Missouri at Kansas City; Director, Children's Mercy Hospital Bioethics Center

Laurence McCullough , PhD, Dalton Tomlin Chair in Medical Ethics and Health Policy, Professor of Medicine and Medical Ethics; Associate Director for Educa on, Center for Medical Ethics and Health Policy, Baylor College of Medicine

William Meadow, MD PhD, Professor of Pediatrics, Co-Director of Neonatology, University of Chicago

Ross McKinney, Jr., MD, Professor of Pediatric Infec ous Diseases; Director, Trent Center for Bioethics, Humani es and History of Medicine, Duke University and School of Medicine

P. Pearl O'Rourke, MD, Director, Human Research A airs, Partners HealthCare

Kathleen E. Powderly, CNM, PhD, Director, John Conley Division of Medical Ethics and Humani es, SUNY Downstate Medical Center

Lainie Friedman Ross, MD, PhD, Carolyn and Ma hew Bucksbaum Professor of Clinical Ethics, Professor, Departments of Pediatrics, Medicine, and Surgery, Co-Director, Ins tute for Transla onal Medicine, Associate Director, MacLean Center for Clinical Medical Ethics, University of Chicago

Richard Sharp, PhD Director of Research Center for Ethics, Humani es and Spiritual Care, Cleveland Clinic

Sadath Sayeed, MD, JD, Assistant Professor of Pediatrics, Global Health and Social Medicine, Harvard Medical School, Sta Neonatologist, Boston Children's Hospital

Jeremy Sugarman, MD, MPH, MA, Harvey M. Meyerho Professor of Bioethics and Medicine, Deputy Director for Medicine, Johns Hopkins Berman Ins tute of Bioethics

Tom Tomlinson, PhD, Director, Center for Ethics and Humani es in the Life Sciences, College of Human Medicine, Michigan State University

Robert D. Truog, MD, Professor of Medical Ethics, Anesthesiology, & Pediatrics, Director of Clinical Ethics, Harvard Medical School; Senior Associate in Critical Care Medicine, Children's Hospital Boston

Yoram T. Unguru, MD, MS, MA, Division of Pediatric Hematology/Oncology, The Herman and Walter Samuelson Children's Hospital at Sinai; Johns Hopkins Berman Ins tute of Bioethics

Kathryn L. Weise, MD, MA, Program Director, Cleveland Fellowship in Advanced Bioethics, Department of Bioethics, Cleveland Clinic

David Woodrum, MD, Professor Emeritus, Neonatology, Dept of Pediatrics, University of Washington School of Medicine, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Ins tute

Stuart Youngner, MD, Professor of Psychiatry and Cogni ve Science, Susan E. Watson Professor of Bioethics, Chair, Department of Bioethics, Case Western Reserve University*

[**individuals who work at the same institutions where the SUPPORT study was conducted*]

cc: The Honorable Kathleen Sibelius, Secretary, Department of Health and Human Services (HHS)

The Honorable Howard K. Koh, Assistant Secretary for Health, HHS

Dr. Francis Collins, Director, Na onal Ins tutes of Health

Dr. Alan E. Gu macher, Director, Eunice Kennedy Shriver Na onal Ins tute of Child Health and Development

Dr. Christopher Aus n, Director, Na onal Center for Advancing Clinical and Transla onal Sciences

Dr Richard B. Marchase, Vice President, Research, University of Alabama at Birmingham

Dr Je rey R Botkin, Chair, Secretary's Advisory Commi ee on Human Research Protec ons

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: FW: an open letter to OHRP about SUPPORT
Date: Friday, May 31, 2013 4:48:00 PM
Attachments: Forwarded Message an open letter to OHRP about SUPPORT.msg

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: William Tarnow-Mordi [mailto:williamtm@med.usyd.edu.au]
Sent: Tuesday, May 28, 2013 10:54 PM
To: Wally Carlo, M.D.; Neil Finer
Cc: Darlow Brian; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: an open letter to OHRP about SUPPORT

Dear Wally and Neil

Brian Darlow and I have accepted an invitation to co-sign a letter from a group of over 20 bioethics leaders and academics with experience in human subjects research to Jerry Menikoff, Director of OHRP.

The letter urges OHRP to reconsider their findings that the institutions involved with the SUPPORT trial failed to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks of enrollment in the study and it asserts that this conclusion was a substantive error that will have adverse implications for future research.

A copy with the original email invitation is attached.

best wishes

William
--
William Tarnow-Mordi
Professor of Neonatal Medicine, Westmead Hospital NHMRC Clinical Trials Centre, University of Sydney,
Foundation Director Westmead International Network for Neonatal Education and Research WINNER Centre -
working together to win healthy survival.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: RE: WSU FOIA request
Date: Friday, May 31, 2013 9:03:00 AM
Attachments: RE WSU FOIA request.msg

Our FOIA folks are looking a

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Mondoro, Traci (NIH/NHLBI) [E]
Sent: Thursday, May 30, 2013 8:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: WSU FOIA request

They don't have to comply, do they? Have their lawyers become involved?

Non Responsive

It is almost Friday.....

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 30, 2013 8:46 PM
To: Mondoro, Traci (NIH/NHLBI) [E]
Subject: Fw: WSU FOIA request

I think haresh is referring to this
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Thursday, May 30, 2013 05:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'Yvonne Vaucher' <yvaucher@ucsd.edu>; 'richard.ehrenkranz@yale.edu' <richard.ehrenkranz@yale.edu>; 'Roger Faix (Roger.Faix@hsc.utah.edu)' <Roger.Faix@hsc.utah.edu>; 'moshea@wfubmc.edu' <moshea@wfubmc.edu>; "Duara, Shahnaz' (SDuara@med.miami.edu)' <SDuara@med.miami.edu>; 'dale_phelps@urmc.rochester.edu' <dale_phelps@urmc.rochester.edu>; 'Frantz, Ivan' <Ivan.Frantz@childrens.harvard.edu>; ' (EMcGowan@tufts-nemc.org)' <EMcGowan@tufts-nemc.org>;

'srhintz@stanford.edu' <srhintz@stanford.edu>; (suhas.kallapur@cchmc.org) <suhas.kallapur@cchmc.org>; Abbot Laptook (alaptook@wihri.org) <alaptook@wihri.org>; Abhik Das (adas@rti.org) <adas@rti.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu) <AnnaMaria.hibbs@cwru.edu>; barbara_stoll@oz.ped.emory.edu <barbara_stoll@oz.ped.emory.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; carl_dangio@urmc.rochester.edu <carl_dangio@urmc.rochester.edu>; Carlton, David P <dpcarlt@emory.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; dstevenson@stanford.edu <dstevenson@stanford.edu>; dwallace@rti.org <dwallace@rti.org>; Ed Bell (edward-bell@uiowa.edu) <edward-bell@uiowa.edu>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; Greg Sokol (gsokol@iupui.edu) <gsokol@iupui.edu>; Haresh Kirpalani (KIRPALANIH@email.chop.edu) <KIRPALANIH@email.chop.edu>; 'John Barks' <jbarks@med.umich.edu>; Jon.E.Tyson@uth.tmc.edu <Jon.E.Tyson@uth.tmc.edu>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Kristi Watterberg (kwatterberg@salud.unm.edu) <kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Luc Brion (luc.brion@utsouthwestern.edu) <luc.brion@utsouthwestern.edu>; Martin Keszler (mkeszler@wihri.org) <mkeszler@wihri.org>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; Meena Garg (mgarg@mednet.ucla.edu) <mgarg@mednet.ucla.edu>; Nelin, Leif <Leif.Nelin@nationwidechildrens.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@utsouthwestern.edu>; Polin, Richard <rap32@mail.cumc.columbia.edu>; Robin Ohls (rohls@salud.unm.edu) <rohls@salud.unm.edu>; ronnie_guillet@urmc.rochester.edu <ronnie_guillet@urmc.rochester.edu>; Satyan Lakshminrusimha <slakshmi@buffalo.edu>; Schmidt, Barbara (Neonatology) <barbara.schmidt@uphs.upenn.edu>; Sood, Beena <bsood@med.wayne.edu>; Truog, William (MD) <wtruog@cmh.edu>; Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU) <UDEVASKAR@mednet.ucla.edu>; Wally Carlo (wacarlo@uab.edu) <wacarlo@uab.edu>

Cc: Archer, Stephanie (NIH/NICHD) [E]; ' (mcunningham@rti.org)' <mcunningham@rti.org>; ' (kzaterka@rti.org)' <kzaterka@rti.org>; 'Petrie, Carolyn' <petrie@rti.org>; Bock, Robert (NIH/NICHD) [E]

Subject: RE: WSU FOIA request

Dear SUPPORT Investigators

WSU received a request from Public Citizen.org for our SUPPORT and TOP IRB forms that we submitted, consent forms, every amendment and continuation and CV of Key personnel.

Have any of you received this request? If so, how are you handling it ?

Let me know ASAP

Thanks

Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 10, 2013 8:30 AM
To: 'nfiner@ucsd.edu'; 'Yvonne Vaucher'; 'richard.ehrenkranz@yale.edu'; 'Roger Faix (Roger.Faix@hsc.utah.edu)'; 'moshea@wfubmc.edu'; "Duara, Shahnaz' (SDuara@med.miami.edu)'; 'dale_phelps@urmc.rochester.edu'; 'Frantz, Ivan'; ' (EMcGowan@tufts-nemc.org)'; 'srhintz@stanford.edu'; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das

(adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); 'John Barks'; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Shankaran, Seetha; Sood, Beena; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; ' (mcunningham@rti.org)'; ' (kzaterka@rti.org)'; 'Petrie, Carolyn'; Bock, Robert (NIH/NICHD) [E]
Subject: REquested items

Hi

Folks have asked for the Masimo letter which is attached. I have also attached the new (October 2012) oxygen management section from the AAP's Guidelines for Perinatal Care.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Friday, May 31, 2013 8:20 AM
To: 'David Magnus'
Subject: RE: Bioethicists' NEJM letter regarding OHRP

Thanks, David - to put it mildly. Francis had sent me a copy of it a few days ago and it is deeply appreciated, both for its impact on SUPPORT and its investigators and on the larger question of research within standard of care. I hope you will find our piece equally helpful.

Best, Alan

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

From: David Magnus [mailto:dmagnus@stanford.edu]
Sent: Friday, May 31, 2013 1:30 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Bioethicists' NEJM letter regarding OHRP

Dr. Guttmacher,

I'm not sure if you have seen this already, but Ben Wilfond and I organized a group of bioethicists and pediatricians to produce a letter protesting the OHRP decision regarding the SUPPORT study--it is scheduled to come out next week alongside the NIH response in NEJM. We plan on sending a version of this letter to Dr. Menikoff (attached). This follows a piece that Art Caplan and I published a couple of weeks ago on the subject, also in NEJM.

Ben said i could share it in anticipation of your visit tomorrow. I look forward to your grand rounds.

Best,

David

David Magnus, PhD
Director, Center for Biomedical Ethics
Thomas A. Raffin Professor of Medicine and Biomedical Ethics and Professor of Pediatrics
Stanford University
dmagnus@stanford.edu
1215 Welch Road, Module A

From: Krisa Van Meurs
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: SUPPORT Study
Date: Thursday, May 30, 2013 10:53:10 AM

Hi Rose,

I thought that you might find this interesting. Any thoughts?

Krisa

Begin forwarded message:

From: "Kathy McClelland" <kathy.mcclelland@stanford.edu>
Subject: FW: SUPPORT Study
Date: May 29, 2013 2:00:43 PM PDT
To: '"Krisa Van Meurs"' <vanmeurs@stanford.edu>

Dear Krisa,

I thought you might like to see this communication that David Magnus forwarded to the IRB.

Kathy

Kathy McClelland - Research Compliance Director
Stanford University, 1501 S. California Ave., MC 5579
Palo Alto, CA 94304 -- kathy.mcclelland@stanford.edu
(650)723-4697 V | (b)(6) C | (650)736-2783 F
http://researchcompliance.stanford.edu/

From: Kathy McClelland [mailto:kathy.mcclelland@stanford.edu]
Sent: Tuesday, May 28, 2013 1:43 PM
To: 'Kathy McClelland'
Subject: SUPPORT Study

Here is a statement from Professor Alex Capron, University of Southern California School of Law, addressing a number of his bioethics colleagues, forwarded to us by David Magnus.
****

From: "Alexander M. Capron" <acapron@law.usc.edu>

Subject: Re: Revised letter to OHRP
Date: May 26, 2013 11:51:44 PM PDT
To: "Norman C. Fost, MD, MPH" <ncfost@pediatrics.wisc.edu

Dear Norm,

Several people have asked questions about OHRP's authority. I believe it is appropriate for us to be very pointed on this issue. The 1981 rules and their reincarnation as the Common Rule place responsibility with the institution and its IRB. OHRP is not given any specific authority. Funding agencies may terminate or suspend funding if the institution has "materially failed to comply with the terms" of the Common Rule. Sec. 46.116 specifies that the basic elements of informed consent include a statement that the study involves research, and explanation of the purposes, the duration of the study, a description of the procedures, and "identification of any procedures which are experimental." For OHRP to issue the opinion that it did here, it would need to have found that all the IRBs that approved SUPPORT had materially failed to exercise their discretion in concluding that the range of "standard" protocols for oxygen saturation that were randomized in SUPPORT were not "experimental" and did not create any risk beyond the risk inherent in the interventions, to which the subjects would have been exposed outside of the research.

In other settings, when an administrative body—in this case, OHRP—can issue sanctions, there is always a process of presenting evidence and making arguments and then a means of appeal. If an institution has a dysfunctional program for human subject protection (which was the central issue at the institutions that OPRR/OHRP have sanctioned in the past), it is not difficult to make a finding that the institution has "materially failed to comply" with the regulations. Otherwise, however, the Common Rule did not set up OHRP as a adjudicatory body, much less as a body with authority to review—and find deficient—the decisions made by institutions, which

otherwise fulfill the assurances they have filed with OHRP, regarding the risks and benefits—and hence, the consent forms—for federally supported research projects. The SUPPORT study is thus both an example of an unsupported (unsupportable) action by OHRP and of the ways in which it is (increasingly—see the Pronovost "check list" QI project in Michigan) attempting to assert an authority that the law (statutory and regulatory) does not give it. The letter is right to push back against this power-grab by OHRP.

Best regards,

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Plummer, Mary (NIH/NICHD) [E]
Subject: SUPPORT council presentation Higgins
Date: Thursday, May 30, 2013 12:57:00 PM
Attachments: SUPPORT Council 2013-06-06 revised 5.24.2012.potx

Here you go
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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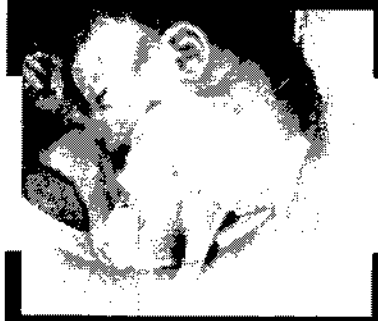
301-496-3790 (FAX)
higginsr@mail.nih.gov



NICHD

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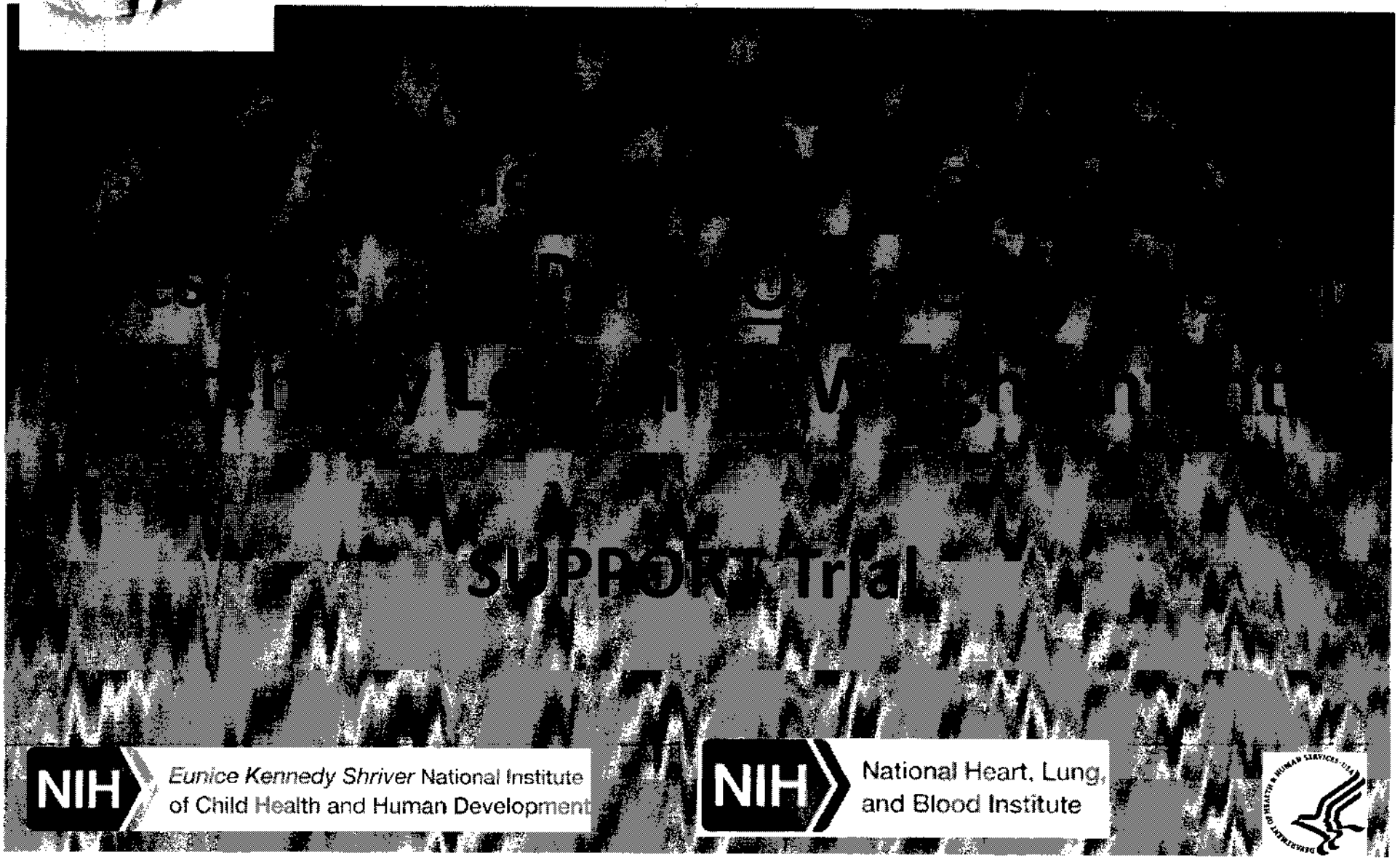
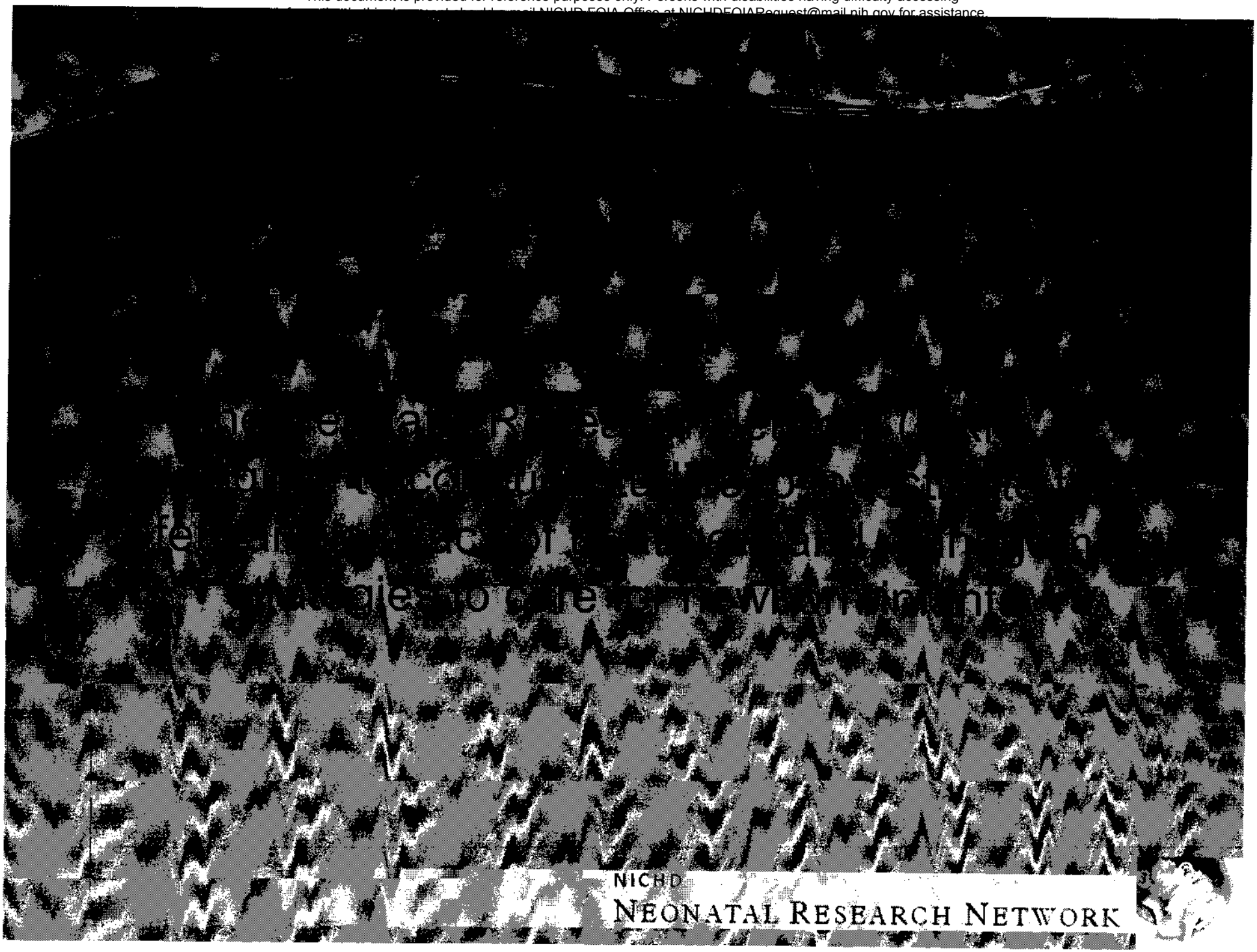
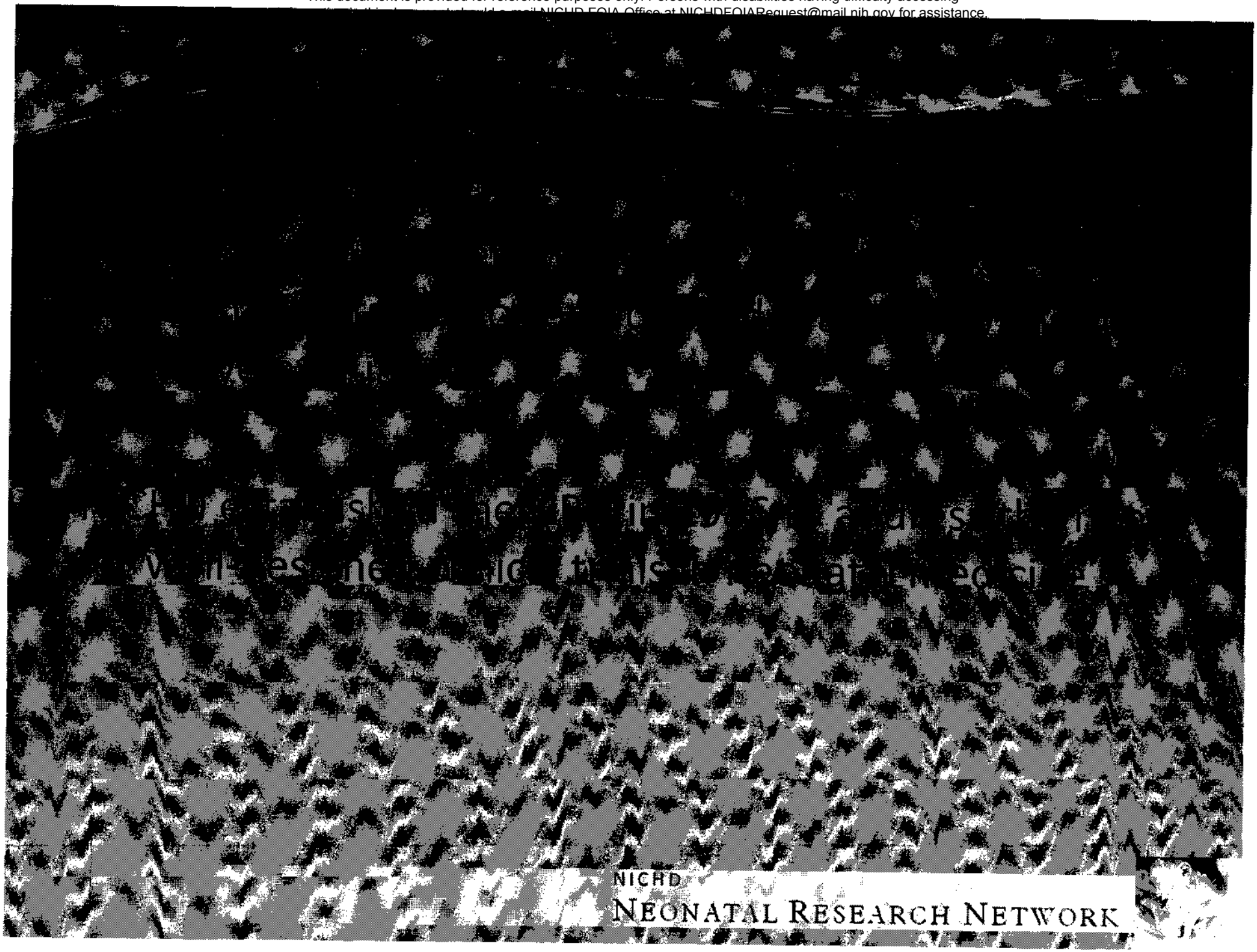


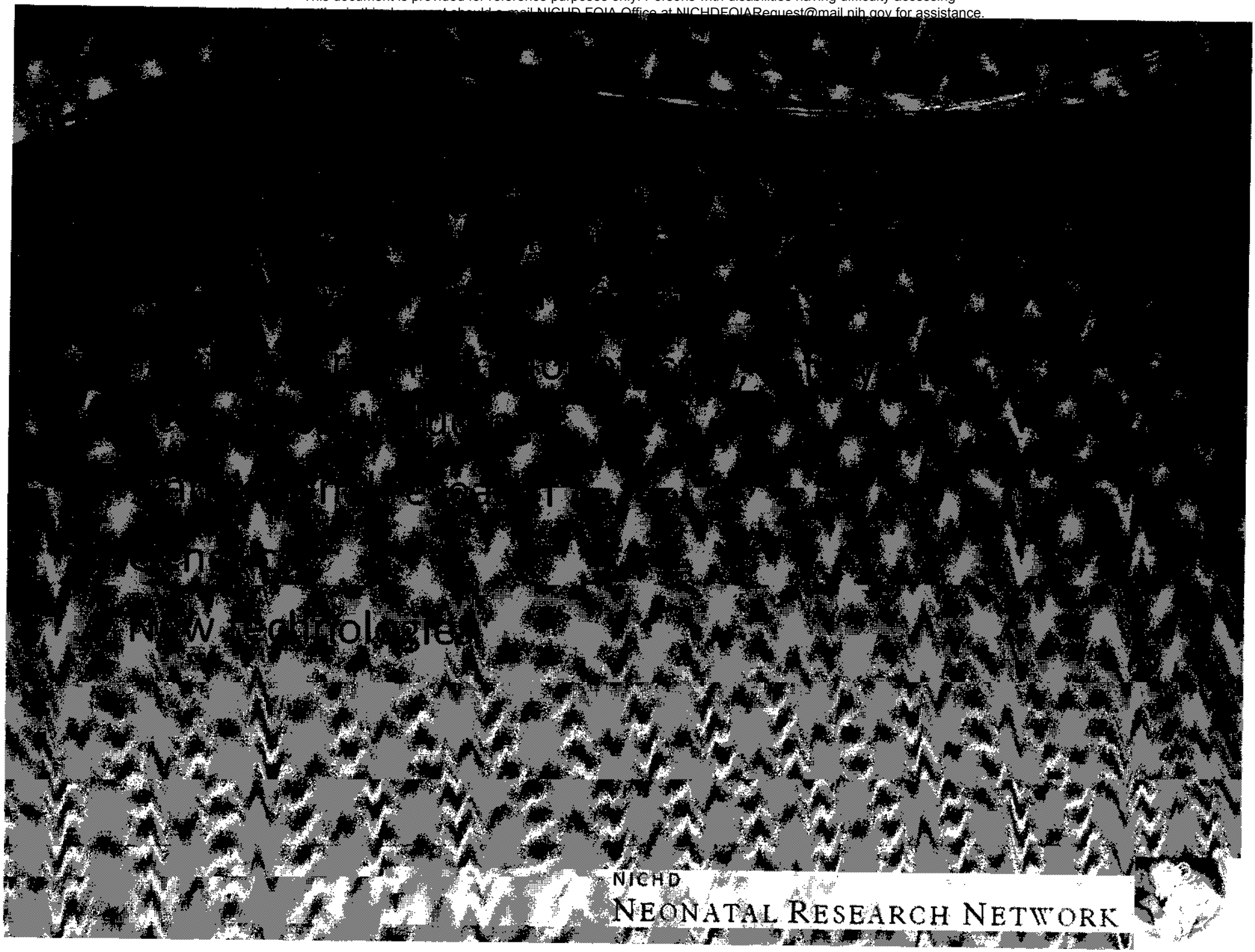
SUPPORT Trial

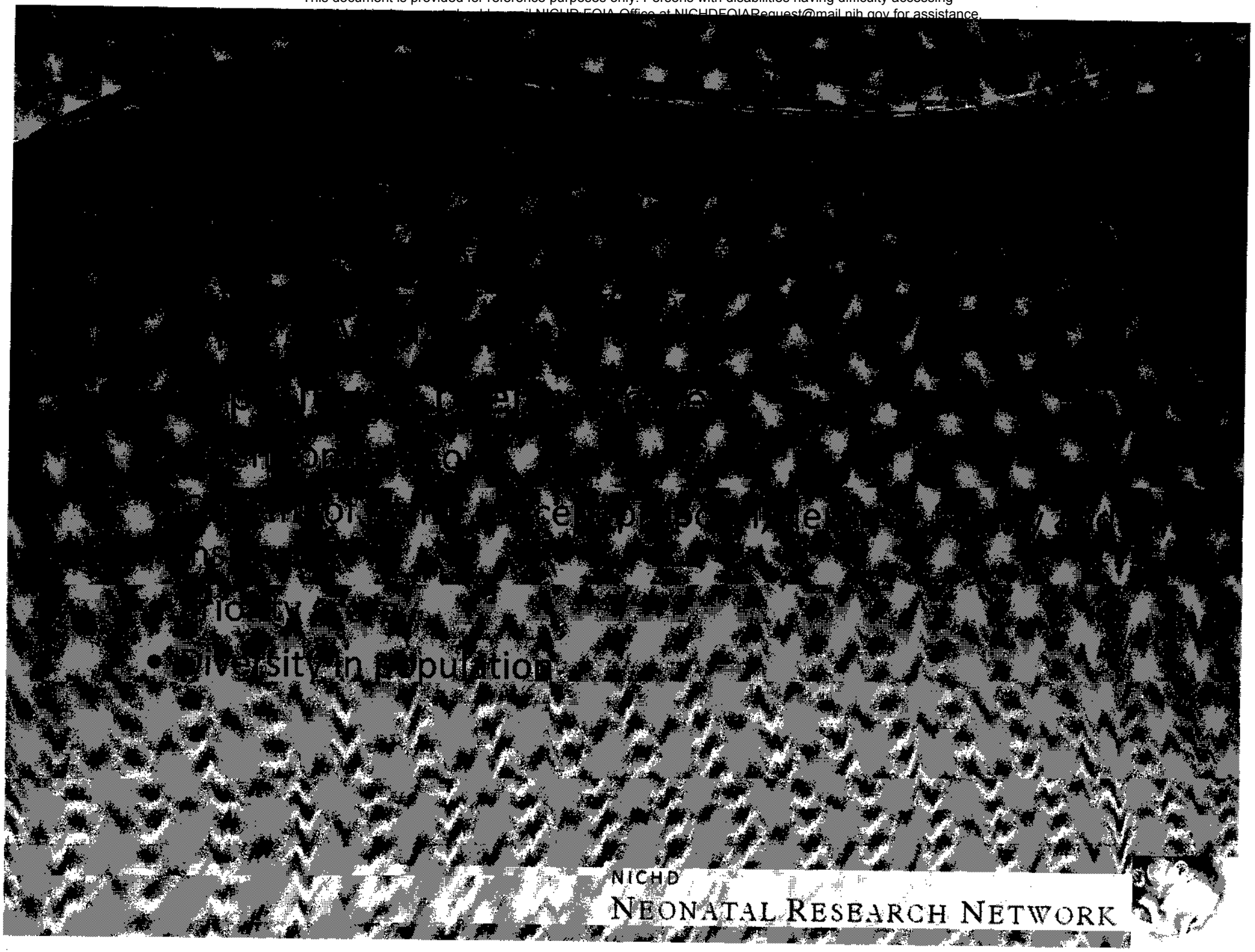
NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

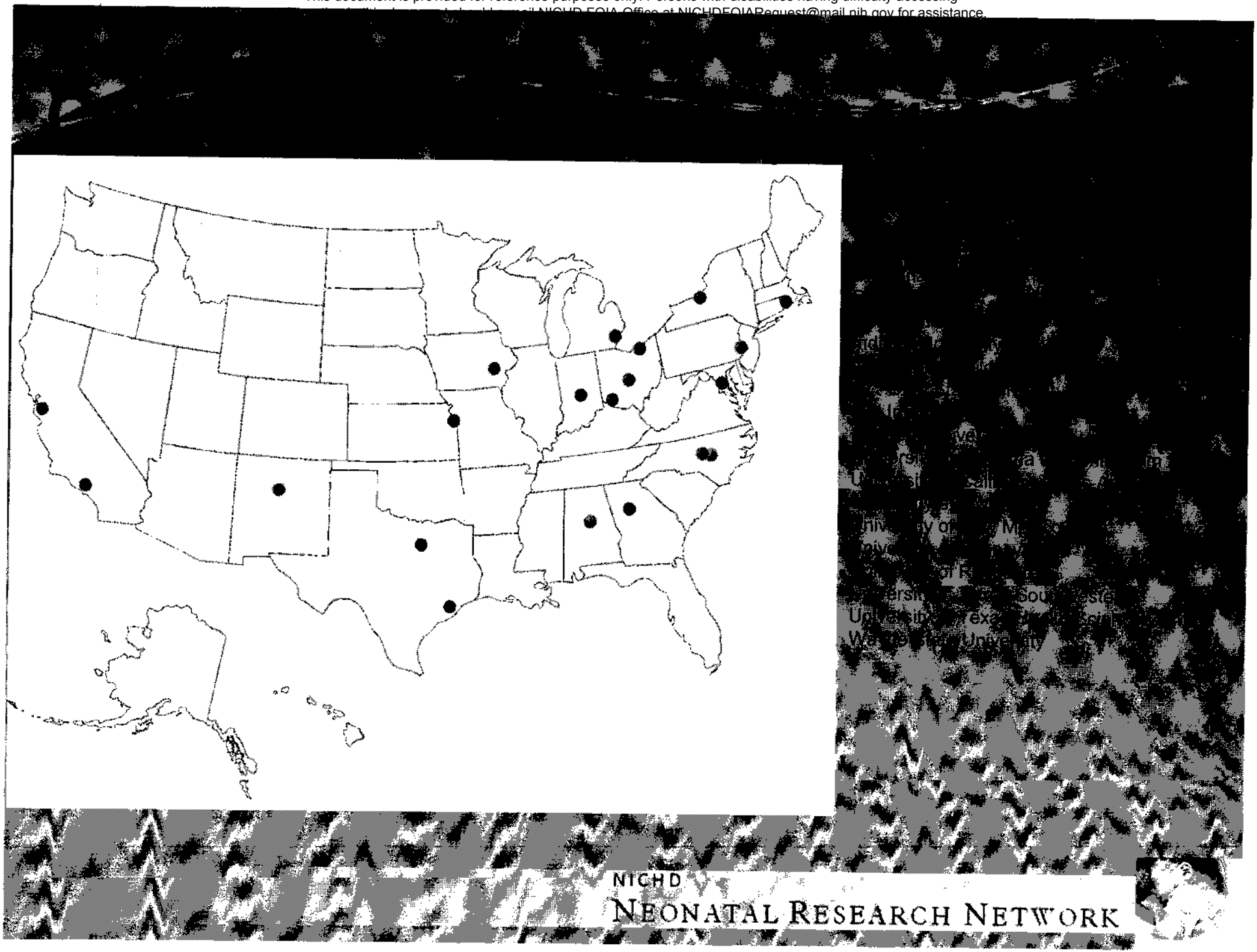
NIH National Heart, Lung, and Blood Institute

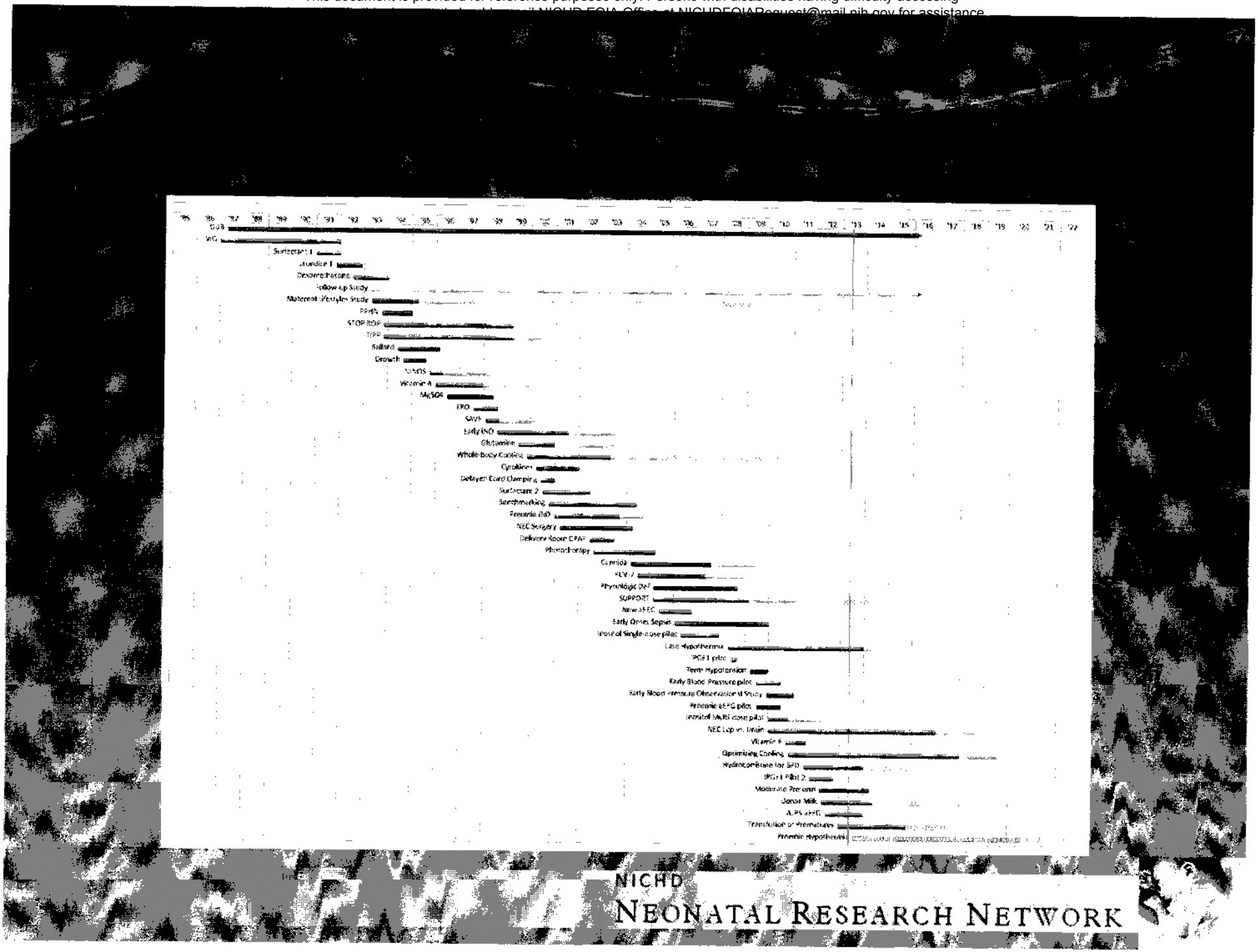


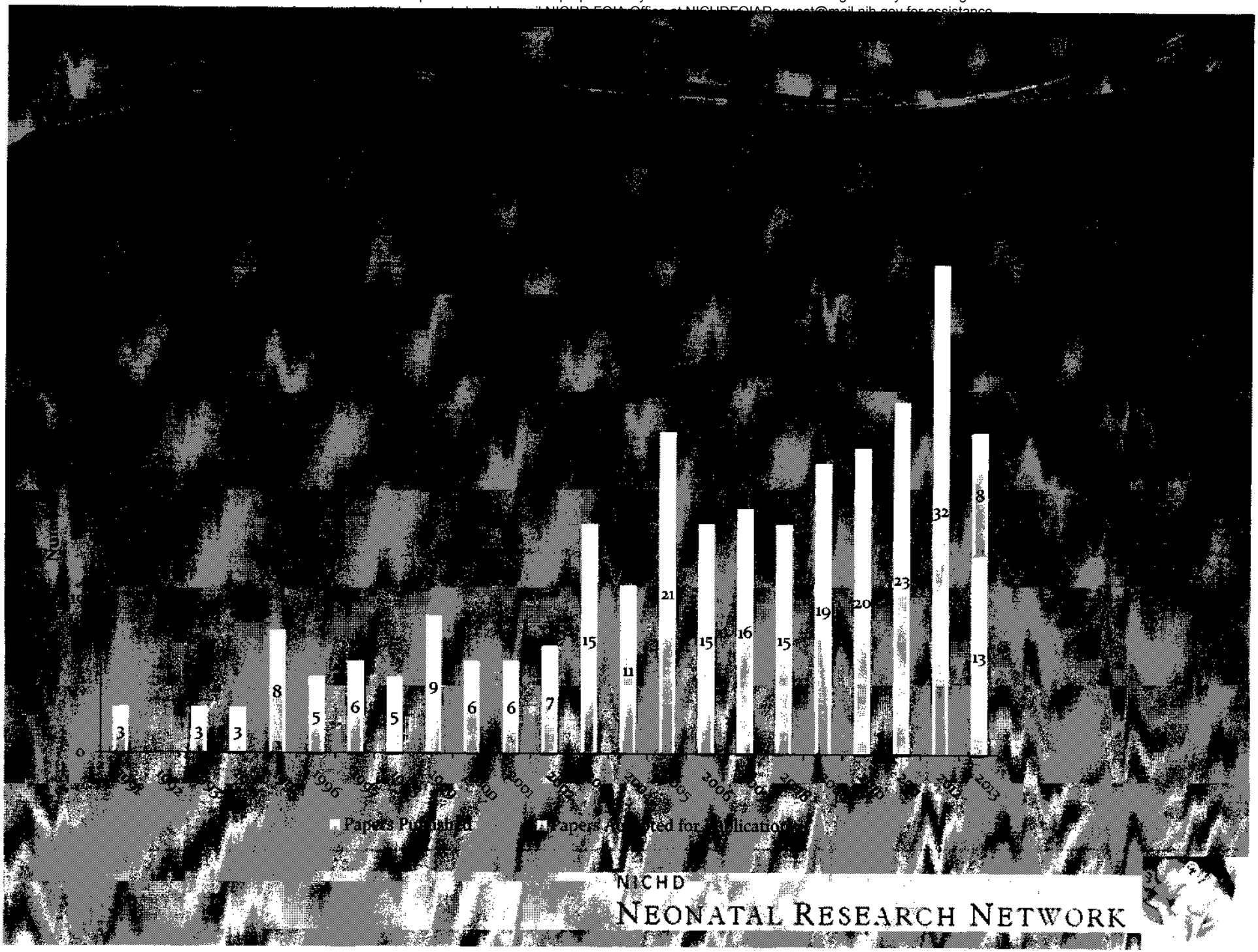


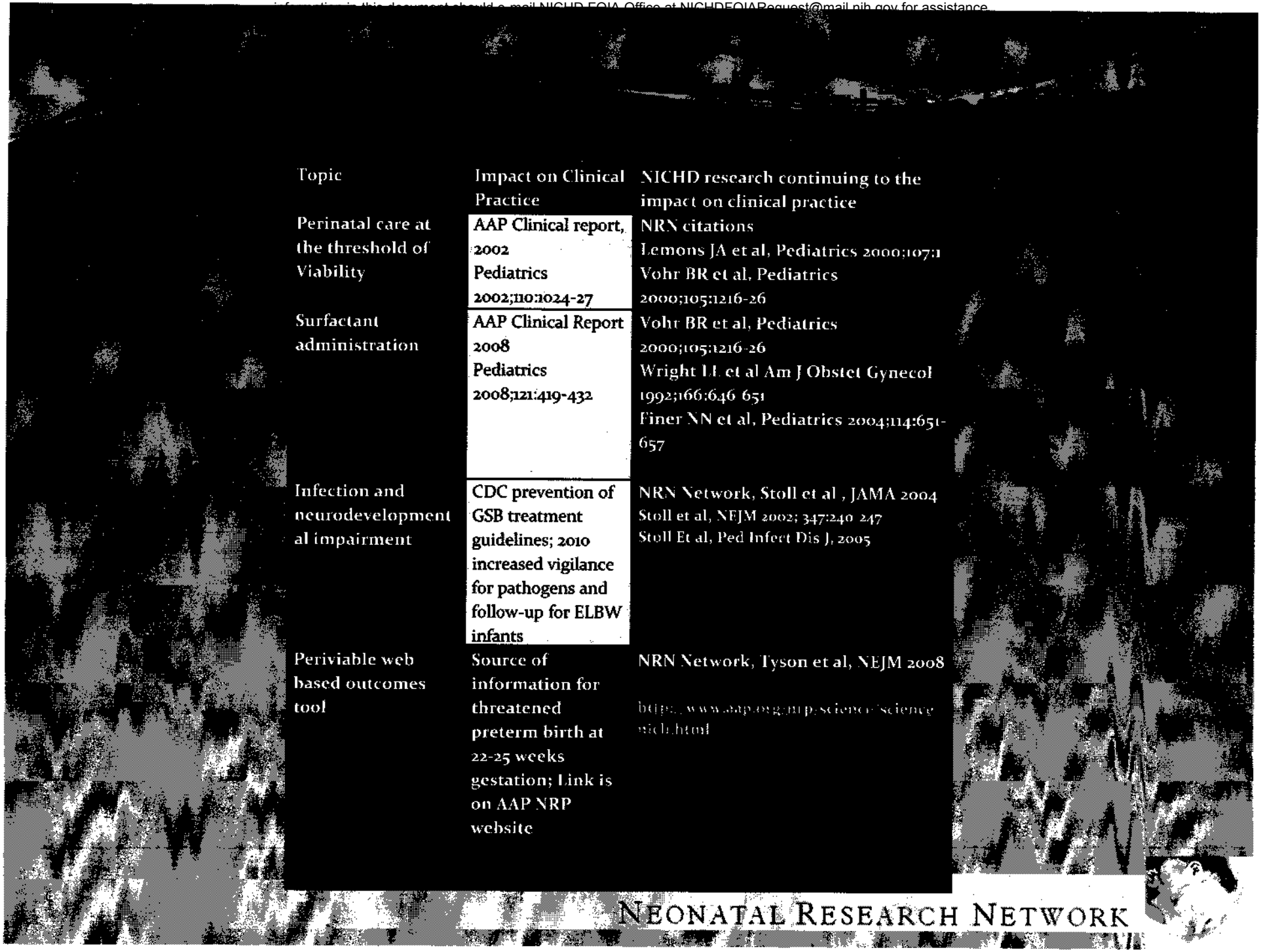










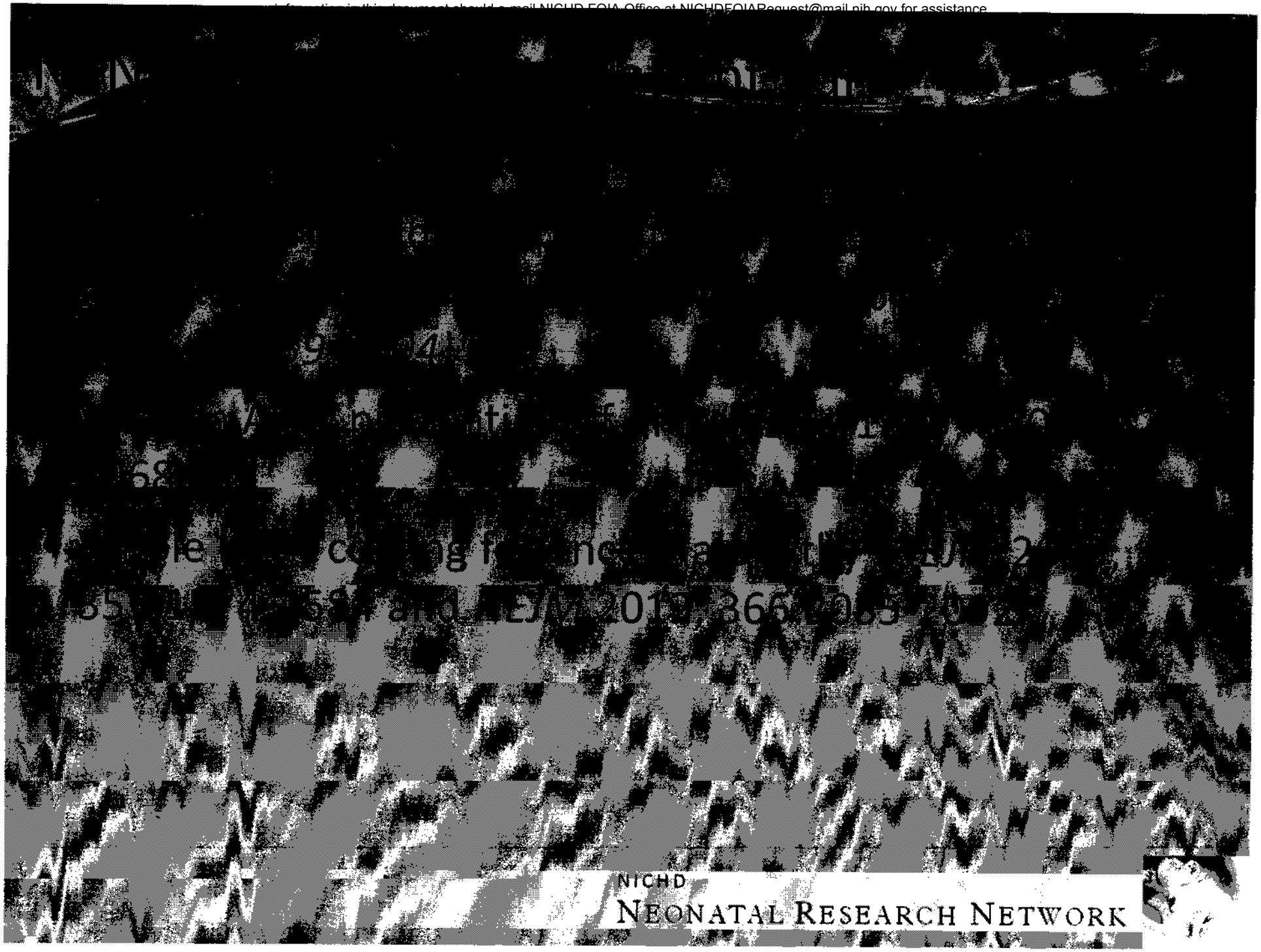


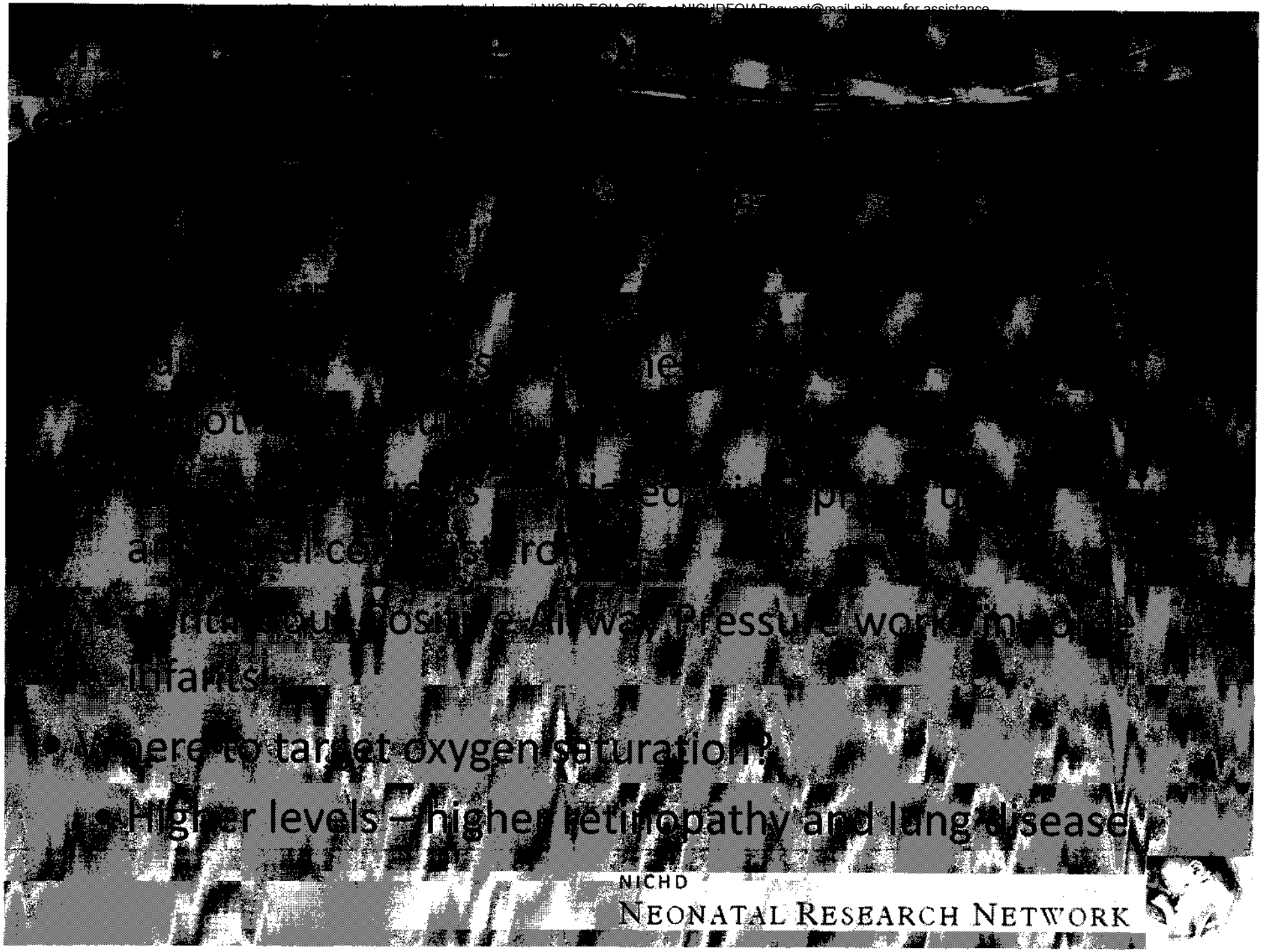
Topic	Impact on Clinical Practice	NICHD research continuing to the impact on clinical practice
Perinatal care at the threshold of Viability	AAP Clinical report, 2002 Pediatrics 2002;110:1024-27	NRN citations Lemons JA et al, Pediatrics 2000;107:1 Vohr BR et al, Pediatrics 2000;105:1216-26
Surfactant administration	AAP Clinical Report 2008 Pediatrics 2008;121:419-432	Vohr BR et al, Pediatrics 2000;105:1216-26 Wright LL et al Am J Obstet Gynecol 1992;166:646-651 Finer NN et al, Pediatrics 2004;114:651-657
Infection and neurodevelopmental impairment	CDC prevention of GSB treatment guidelines; 2010 increased vigilance for pathogens and follow-up for ELBW infants	NRN Network, Stoll et al , JAMA 2004 Stoll et al, NEJM 2002; 347:240-247 Stoll Et al, Ped Infect Dis J, 2005
Periviable web based outcomes tool	Source of information for threatened preterm birth at 22-25 weeks gestation; Link is on AAP NRP website	NRN Network, Tyson et al, NEJM 2008 http://www.aap.org/nrp/sciencescience.html

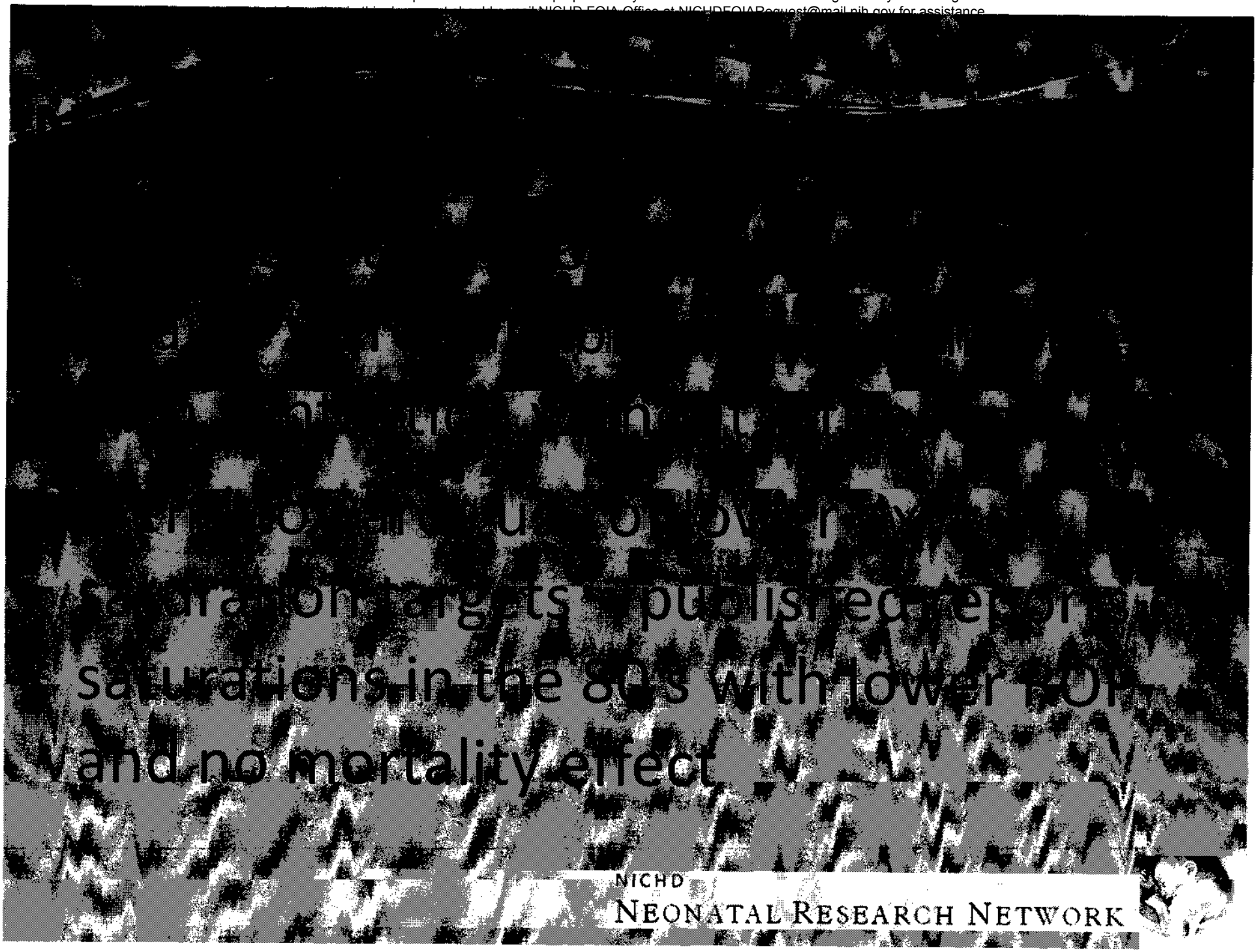
NEONATAL RESEARCH NETWORK

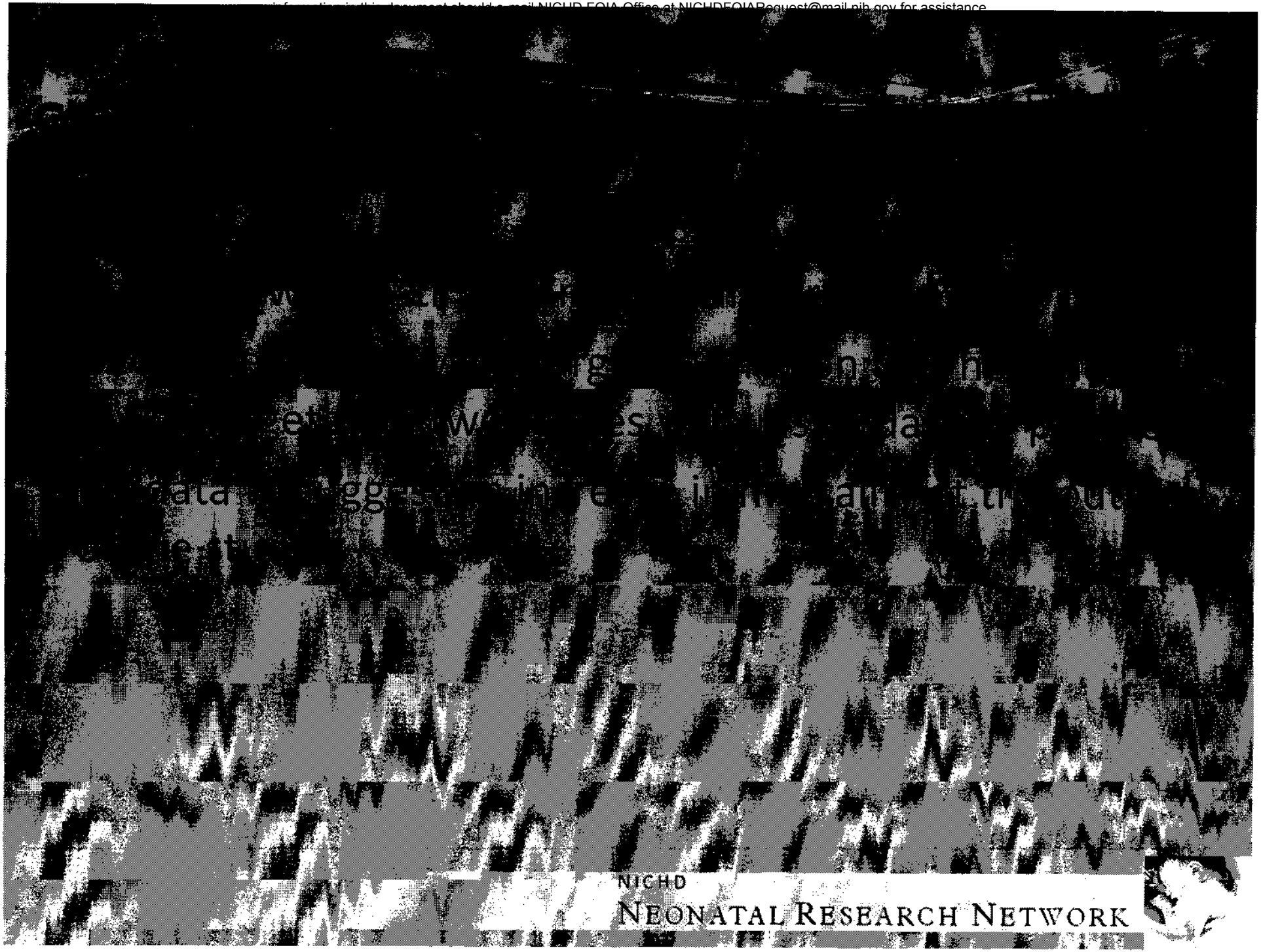
Topic	Impact on Clinical Practice	NICHD research continuing to the impact on clinical practice
Levels of neonatal care	AAP Policy Statement: Classification and organization of neonatal facilities to care for NICU patients, Pediatrics 2004;1141341-47	Lemons JA et al, Pediatrics 2000;107:1
Follow up of high risk infants	AAP Policy Statement: Hospital discharge of the high-risk neonate, Pediatrics 2008;122:1119-1126	Vohr et al, Pediatrics 2004;114 (5 suppl):1377-1397 Vohr BR et al, Semin Perinatol 2003;27:333-342
Post natal Steroids	AAP Policy Statement: Postnatal Corticosteroids to prevent or treat BPD, Pediatrics 2010;126:800-808	Walsh MC et al, Pediatrics 2007;119:876-890 Vohr BR et al, Pediatrics 2005;116:635-643 Walsh MC et al, Pediatrics 2006; epages 118/5/e1328 Wilson-Costello D et al, Pediatrics 2009 epages 123/3/e430
Antenatal corticosteroids	ACOG Committee Opinion Number 475: Antenatal Corticosteroid Therapy for Fetal Maturations. Obstetrics and Gynecology 2011;117:422-424.	Lee BH et. al, Pediatrics 2008;121:289-96.
Breast Feeding	AAP Policy Statement on Breast feeding 2013	Vohr BR Pediatrics 2006, Vohr BR Pediatrics 2007, Meinzen-Derr J Perinatology 2009, Hintz SR Pediatrics 2005

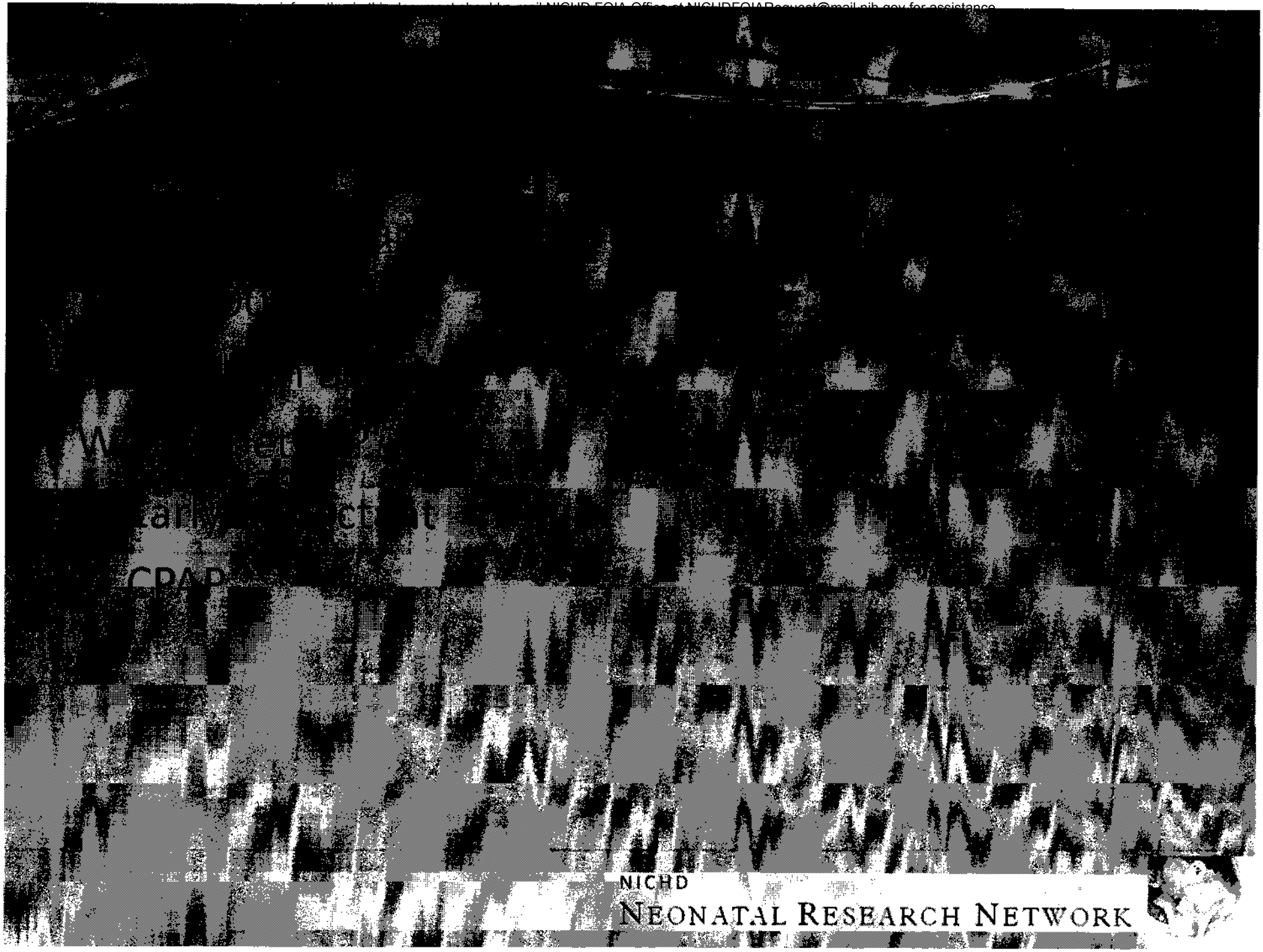
NICHD
NEONATAL RESEARCH NETWORK

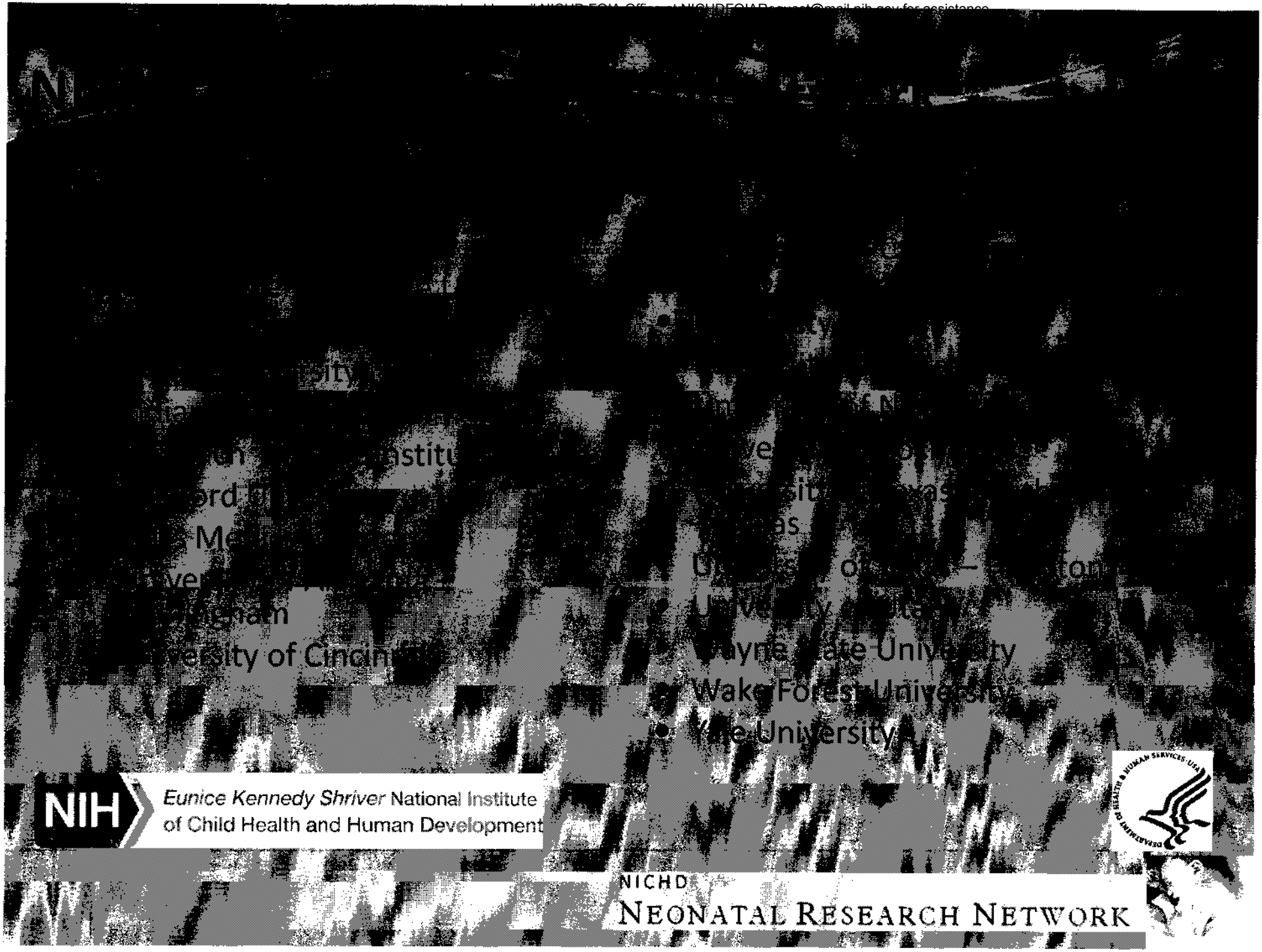












From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Subject: RE: an open letter to OHRP about SUPPORT
Date: Wednesday, May 29, 2013 4:30:00 PM

Do you know if there will be an on-line first article by Drs. Guttmacher and Collins today in NEJM??

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, May 29, 2013 4:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: an open letter to OHRP about SUPPORT

It looks like I was blind cc'd.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 29, 2013 4:19 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: an open letter to OHRP about SUPPORT

How
Did you get this?

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, May 29, 2013 4:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: an open letter to OHRP about SUPPORT

FYI.
-----Original Message-----
From: Lantos, John [mailto:jlantos@cmh.edu]
Sent: Tuesday, May 28, 2013 7:13 AM
To: wlm1@uchicago.edu; brian.darlow@otago.ac.nz; keith.barrington@umontreal.ca; williamtm@med.usyd.edu.au; askie@ctc.usyd.edu.au
Subject: an open letter to OHRP about SUPPORT

Friends,

A group of folks in the US, mostly bioethicists, some pediatricians, have written a letter to OHRP. It was, as you might imagine, a long process to get some consensus about language among this feisty group. We've finally agreed about what the letter should say.

We want to send it tomorrow afternoon. We are hoping that either the NEJM or JAMA will agree to run it as an ePub before print this week.

I'm writing to ask if you are interested in adding your names to the list of people who have signed it. We have decided not to have anyone who was directly involved in SUPPORT and so have very few neonatologists on the list.

If you are interested, send me a note, and let me know how you'd like your title and affiliation to be listed. You could ask others, too, if you'd like.

Note: at this point, we cannot change the letter, because this is what went out and what - after long discussions - people have agreed to sign on to.

John
John D. Lantos M.D.
816-701-5284

From: Luc Brion
To: Bell, Edward (Pediatrics); Nellie Hansen; Richard Ehrenkranz; Kathleen Kennedy; Michele Walsh; Seetha Shankaran; Mike Acarregui; Johnson, Karen (Pediatrics); Ellen Hale; Lynn Messina; Meg Cunningham; Abbot Laptook; Ron Goldberg; Krisa VanMeurs; Wally Carlo; Brenda Poindexter; Roger Faix; David Carlton; Kristi Watterberg; Dan Ellsbury (gmail); Abhik Das; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Thank you for your manuscript submission to Pediatrics
Date: Wednesday, May 29, 2013 12:57:16 PM

Thanks a lot!
Luc

From: Bell, Edward (Pediatrics) [edward-bell@uiowa.edu]
Sent: Wednesday, May 29, 2013 11:36 AM
To: Nellie Hansen; Luc Brion; Richard Ehrenkranz; Kathleen Kennedy; Michele Walsh; Seetha Shankaran; Mike Acarregui; Johnson, Karen (Pediatrics); Ellen Hale; Lynn Messina; Meg Cunningham; Abbot Laptook; Ron Goldberg; Krisa VanMeurs; Wally Carlo; Brenda Poindexter; Roger Faix; David Carlton; Kristi Watterberg; (b)(6) (b)(6) (gmail); Abhik Das; Rosemary Higgins
Cc: Stephanie Archer
Subject: FW: Thank you for your manuscript submission to Pediatrics

-----Original Message-----
From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com [mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of PediatricsEditorial@aap.org
Sent: Wednesday, May 29, 2013 11:28 AM
To: Bell, Edward (Pediatrics)
Subject: Thank you for your manuscript submission to Pediatrics

29-May-2013

Manuscript ID: 2013-1684
Serum Tocopherol Levels in Very Preterm Infants After a Single Enteral Dose of Vitamin E at Birth

Dear Dr. Edward Bell:

Thank you for submitting your article(s) to Pediatrics. This is an automated reply. If there are problems or questions, we will contact you by email.

If you submitted a new MANUSCRIPT, it will be screened and possibly peer-reviewed. The peer-review process may take eight weeks or more. If your manuscript is accepted, it will be published online. The Editors determine later if an accepted paper also will appear in the print edition. All accepted Case Reports are published online only.

If you submitted a SUPPLEMENT (single article or multiple articles), it will be peer-reviewed. You will be notified of a decision within approximately two months.

If you submitted a REVISED manuscript or supplement, your submission retains its previous ID number but is appended with ".R1" or ".R2" depending on the version.

You can review the status of your submission online by logging in at http://mc.manuscriptcentral.com/pediatrics and checking your author center.

We will contact you as soon as possible with our decision.

Sincerely,
Lewis R. First, MD
Editor-in-Chief
Pediatrics Editorial Office
University of Vermont College of Medicine
89 Beaumont Ave, Given D201
Burlington, VT 05405-0068
Telephone: 802.656.2505
Email: PediatricsEditorial@aap.org

http://mc.manuscriptcentral.com/pediatrics

UT Southwestern Medical Center
The future of medicine, today.

From: Pablo Sanchez
To: Gabrio, Jenna
Cc: Cunningham, Meg; Lewis-Evans, Amanda; alaptook@WIHRI.org; ahensman@wihri.org; Bradley Yoder; Das, Abhik; Diana Vasil; Eggleston, Barry; Higgins, Rosemary (NIH/NICHD) [E]; Joanna Beachy; Matt Laughon; Roger.Faix@hsc.utah.edu; Roy Heyne; sshankar@med.wayne.edu; DysartK@email.chop.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Huitema, Carolyn Petrie; lmoore@med.wayne.edu; Zaterka-Baxter, Kristin
Subject: Re: Preemie Hypothermia Subcommittee Call (5/29, Wednesday, 11:00AM ET)
Date: Wednesday, May 29, 2013 10:16:29 AM

I am sorry but on service and on rounds

Pablo
(b)(6) (cell)
(beeper)
214-648-3903 (office)

Sent from iPhone.

On May 29, 2013, at 8:40 AM, "Gabrio, Jenna" <jgabrio@rti.org> wrote:

> A friendly reminder for today's call.
>
> **From:** Cunningham, Meg
> **Sent:** Friday, May 24, 2013 2:31 PM
> **To:** Lewis-Evans, Amanda; 'Abbot Laptook (alaptook@WIHRI.org)'; 'ahensman@wihri.org'; 'Bradley Yoder'; Das, Abhik; 'Diana Vasil'; Eggleston, Barry; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Joanna Beachy'; 'Matt Laughon'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Roger.Faix@hsc.utah.edu'; 'Roy.Heyne@utsouthwestern.edu'; 'sshankar@med.wayne.edu'; 'DysartK@email.chop.edu'
> **Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Gabrio, Jenna; Huitema, Carolyn Petrie; 'lmoore@med.wayne.edu'; Zaterka-Baxter, Kristin
> **Subject:** RE: Preemie Hypothermia Subcommittee Call (5/29, Wednesday, 11:00AM ET)
>
> Hi All,
>
> Attached are draft forms, sample consent form and updated protocol to review for the call on Wednesday.
>
> Thanks,
> Meg
>
> **From:** Lewis-Evans, Amanda
> **Sent:** Thursday, May 23, 2013 9:45 AM
> **To:** 'Abbot Laptook (alaptook@WIHRI.org)'; 'ahensman@wihri.org'; 'Bradley Yoder'; Das, Abhik; 'Diana Vasil'; Eggleston, Barry; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Joanna Beachy'; 'Matt Laughon'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Roger.Faix@hsc.utah.edu'; 'Roy.Heyne@utsouthwestern.edu'; 'sshankar@med.wayne.edu'; DysartK@email.chop.edu
> **Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; 'lmoore@med.wayne.edu'; Zaterka-Baxter, Kristin; Lewis-Evans, Amanda
> **Subject:** Preemie Hypothermia Subcommittee Call (5/29, Wednesday, 11:00AM ET)

Dear all,

The Preemie Hypothermia Subcommittee Call has been scheduled for:

Wednesday, 5/29
11:00am ET

Dial:
Within the USA
(b)(6)

or

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Thanks,

Amanda

From: Lewis-Evans, Amanda
Sent: Tuesday, May 14, 2013 9:48 AM
To: Abbot Laptook (alaptook@WIHRI.org); 'ahensman@wihri.org'; Bradley Yoder; Das, Abhik; Diana Vasil; Eggleston, Barry; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Joanna Beachy'; 'Matt Laughon'; Pablo.Sanchez@UTSouthwestern.edu; Roger.Faix@hsc.utah.edu; Roy.Heyne@utsouthwestern.edu; 'sshankar@med.wayne.edu'
Cc: 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; 'lmoore@med.wayne.edu'; Zaterka-Baxter, Kristin; Lewis-Evans, Amanda (alewis@rti.org)
Subject: Preemie Hypothermia Subcommittee Call - Availability Request

Hi folks,

We would like to schedule a Preemie Hypothermia call to discuss forms and the consent form.

Please provide your availability for the following dates via email or Doodle poll (link below).

Doodle Poll Link: http://doodle.com/hpkeywb49scmezta

5/20, M
5/21, Tu
5/22, W

5/23, Th
5/24, F

5/28, Tu
5/29, W
5/30, Th
5/31, F

6/3, M
6/4, Tu
6/5, W
6/6, Th
6/7, F

Thanks,

Amanda

UT Southwestern Medical Center
The future of medicine, today.

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: an open letter to OHRP about SUPPORT
Date: Wednesday, May 29, 2013 9:54:35 AM

It is really (b)(5) I know that this has been (b)(5)
(b)(5)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 29, 2013 8:10 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: FW: an open letter to OHRP about SUPPORT

As an FYI
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: William Tarnow-Mordi [mailto:williamtm@med.usyd.edu.au]
Sent: Tuesday, May 28, 2013 10:54 PM
To: Wally Carlo, M.D.; Neil Finer
Cc: Darlow Brian; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: an open letter to OHRP about SUPPORT

Dear Wally and Neil

Brian Darlow and I have accepted an invitation to co-sign a letter from a group of over 20 bioethics leaders and academics with experience in human subjects research to Jerry Menikoff, Director of OHRP.

The letter urges OHRP to reconsider their findings that the institutions involved with the SUPPORT trial failed to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks of enrollment in the study and it asserts that this conclusion was a substantive error that will have adverse implications for future research.

A copy with the original email invitation is attached.

best wishes

William
--
William Tarnow-Mordi
Professor of Neonatal Medicine, Westmead Hospital NHMRC Clinical Trials Centre, University of Sydney, Foundation Director Westmead International Network for Neonatal Education and Research WINNER Centre - working together to win healthy survival.

From: Schmidt, Barbara (Neonatology)
To: Brocklehurst, Peter; Kylie Hunter; William Tarnow Mordi; Colin Morley; Lex Doyle; Peter Graham Davis; ccole@jhu.edu; John Simes; Brian Darlow; peter.brocklehurst@npeu.ox.ac.uk; Henry Halliday; Marlow, Neil; win.tin@stees.nhs.uk; ben.stenson@luht.scot.nhs.uk; Jayne.Tierney@ctu.mrc.ac.uk; Robin Roberts; Robin Whyte; Lorrie Costantini; Christian Poets; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; adas@rti.org; wrich@ucsd.edu; WCarlo@peds.uab.edu
Cc: Lisa Askie
Subject: RE: Paper by members of BOOST-II UK DMC on interim data sharing
Date: Wednesday, May 29, 2013 8:30:24 AM

Thank you, Peter and Ben.

On a related but different topic: I have not forgotten about the draft joint statement from Neoprom that Brian circulated after PAS: My institution is still pondering over the wording. I will contact all of you after I hear back from them.
Barbara

-----Original Message-----
From: Brocklehurst, Peter [mailto:p.brocklehurst@ucl.ac.uk]
Sent: Wed 5/29/2013 3:59 AM
To: Schmidt, Barbara (Neonatology); Kylie Hunter; William Tarnow Mordi; Colin Morley; Lex Doyle; Peter Graham Davis; ccole@jhu.edu; John Simes; Brian Darlow; peter.brocklehurst@npeu.ox.ac.uk; Henry Halliday; Marlow, Neil; win.tin@stees.nhs.uk; ben.stenson@luht.scot.nhs.uk; Jayne.Tierney@ctu.mrc.ac.uk; Robin Roberts; Robin Whyte; Lorrie Costantini; Christian Poets; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; adas@rti.org; wrich@ucsd.edu; WCarlo@peds.uab.edu
Cc: Lisa Askie
Subject: RE: Paper by members of BOOST-II UK DMC on interim data sharing

Dear Barbara

Ben has pointed out that my email yesterday contained a grammatical error - too many negatives in one of the sentences. Many apologies for this. For completeness I have included the amended (and correct text) below:

Thank you for your message. The reference to the paper by Iain Chalmers has now been removed from the NPEU website materials about the BOOST II UK trial. And we have updated this reading list by adding the COT paper. As I have said in previous correspondence with you, and as Ben Stenson and Neil Marlow have said to you in person, the BOOST II trial DMC acted independently in publishing their paper and neither the trial investigators, nor the Trial Steering Committee were involved in it. In the NEJM paper about the BOOST trials we said that "Consensus is needed about the roles of data and safety monitoring committees of simultaneous, similar, independent trials in respect to patient safety". We included this content in the paper because it was clear that not all of the trials were involved in the analysis. The sentence is not critical and was intended to acknowledge that the best approach is not established. We do accept that the COT Trial Steering Committee and DSMB strongly disagreed with the scientific and methodological arguments that led to our interim subgroup analysis by oximeter software and we are not critical of your ethical standards.

With best wishes

Peter

-----Original Message-----
From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: 27 May 2013 18:40
To: Brocklehurst, Peter; Kylie Hunter; William Tarnow Mordi; Colin Morley; Lex Doyle; Peter Graham Davis; ccole@jhu.edu; John Simes; Brian Darlow; peter.brocklehurst@npeu.ox.ac.uk; Henry Halliday; Marlow, Neil; win.tin@stees.nhs.uk; ben.stenson@luht.scot.nhs.uk; Jayne.Tierney@ctu.mrc.ac.uk; Robin Roberts; Robin Whyte; Lorrie Costantini; Christian Poets; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; adas@rti.org; wrich@ucsd.edu; WCarlo@peds.uab.edu
Cc: Lisa Askie
Subject: RE: Paper by members of BOOST-II UK DMC on interim data sharing

Dear Peter, Ben and Neil,

All three of you have reassured us - in writing or in person - that the BOOST II UK investigators were not aware of Iain Chalmer's published attack on the COT Steering Committee. In fact, one of the pledges during the May 6th Neoprom meeting was that the BOOST II UK investigators would discuss if and how to distance themselves from this publication. I was therefore surprised to see that the NPEU recommends Iain's paper to clinicians under "Further Reading" on its public BOOST II website:

https://www.npeu.ox.ac.uk/boost/clinician-updates <https://www.npeu.ox.ac.uk/boost/clinician-updates>

Why can we not simply accept that we strongly disagree - since 2010 - on the scientific and methodological arguments that led to your interim subgroup analysis by oximeter software?

Why do the BOOST II UK investigators and DSMB find it necessary to attack the ethical standards and reputation of the members of the COT SC and DSMB?

Barbara

From: Brocklehurst, Peter [mailto:p.brocklehurst@ucl.ac.uk <mailto:p.brocklehurst@ucl.ac.uk>]

Sent: Fri 26/04/2013 10:18 AM

To: Schmidt, Barbara (Neonatology); Kylie Hunter; William Tarnow Mordi; Colin Morley; Lex Doyle; Peter Graham Davis; ccole@jhu.edu <mailto:ccole@jhu.edu> ; John Simes; Brian Darlow; peter.brocklehurst@npeu.ox.ac.uk <mailto:peter.brocklehurst@npeu.ox.ac.uk> ; Henry Halliday; Marlow, Neil; win.tin@stees.nhs.uk <mailto:win.tin@stees.nhs.uk> ; ben.stenson@luht.scot.nhs.uk <mailto:ben.stenson@luht.scot.nhs.uk> ; Jayne.Tierney@ctu.mrc.ac.uk <mailto:Jayne.Tierney@ctu.mrc.ac.uk> ; Robin Roberts; Robin Whyte; Lorrie Costantini; Christian Poets; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org <mailto:kzaterka@rti.org> ; adas@rti.org <mailto:adas@rti.org> ; wrich@ucsd.edu <mailto:wrich@ucsd.edu> ; WCarlo@peds.uab.edu <mailto:WCarlo@peds.uab.edu>

Cc: Lisa Askie

Subject: RE: Paper by members of BOOST-II UK DMC on interim data sharing

Dear Barbara

I just wanted to write to let you know that none of the BOOST-II UK investigators were involved with the publication in Trials which was authored by our independent Data Monitoring Committee. We were aware that they were writing a paper about the issue of data sharing and data monitoring committees, but we were not party to the content. We were told recently that its publication was imminent, but by then it was already in press.

We hope that this publication does not adversely affect the NeOProM collaboration. We remain absolutely committed to contributing all our data to the collaboration at the end of the trials, and I hope this will continue as planned.

With best wishes

Peter

-----Original Message-----

From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu <mailto:barbara.schmidt@uphs.upenn.edu>]

Sent: 26 April 2013 08:11

To: Kylie Hunter; William Tarnow Mordi; Colin Morley; Lex Doyle; Peter Graham Davis; ccole@jhu.edu <mailto:ccole@jhu.edu> ; John Simes; Brian Darlow; peter.brocklehurst@npeu.ox.ac.uk <mailto:peter.brocklehurst@npeu.ox.ac.uk> ; Henry Halliday; Marlow, Neil; win.tin@stees.nhs.uk <mailto:win.tin@stees.nhs.uk> ; ben.stenson@luht.scot.nhs.uk <mailto:ben.stenson@luht.scot.nhs.uk> ; Jayne.Tierney@ctu.mrc.ac.uk <mailto:Jayne.Tierney@ctu.mrc.ac.uk> ; Robin Roberts; Robin Whyte; Lorrie

Costantini; Christian Poets; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org <mailto:kzaterka@rti.org> ; adas@rti.org <mailto:adas@rti.org> ; wrich@ucsd.edu <mailto:wrich@ucsd.edu> ; WCarlo@peds.uab.edu <mailto:WCarlo@peds.uab.edu>

Cc: Lisa Askie

Subject: AW: Paper by members of BOOST-II UK DMC on interim data sharing

Good mornig,

This is an extraordinary document that will do little to strenghthen an already fragile collaboration. The COT SC will commence its deliberations next week to formulate our response in a professional manner that nevertheless sets the record straight.

Barbara

-----Ursprüngliche Nachricht-----

Von: Kylie Hunter [mailto:kylie.hunter@ctc.usyd.edu.au <mailto:kylie.hunter@ctc.usyd.edu.au> <mailto:kylie.hunter@ctc.usyd.edu.au%20%3cmailto:kylie.hunter@ctc.usyd.edu.au%3e%20>]

Gesendet: Do 25.04.2013 19:21

An: William Tarnow Mordi; 'Colin Morley'; 'Lex Doyle'; 'Peter Graham Davis'; 'ccole@jhu.edu'; John Simes; 'Brian Darlow'; 'peter.brocklehurst@npeu.ox.ac.uk'; 'Henry Halliday'; 'n.marlow@ucl.ac.uk'; 'win.tin@stees.nhs.uk'; 'ben.stenson@luht.scot.nhs.uk'; 'Jayne.Tierney@ctu.mrc.ac.uk'; Schmidt, Barbara (Neonatology); 'Robin Roberts'; 'Robin Whyte'; 'Lorrie Costantini'; 'Christian Poets'; 'Finer, Neil'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kzaterka@rti.org'; 'adas@rti.org'; 'wrich@ucsd.edu'; 'WCarlo@peds.uab.edu'

Cc: Lisa Askie

Betreff: Paper by members of BOOST-II UK DMC on interim data sharing

Dear NeOProM Collaborators,

Please find attached the following article for your information:

Chalmers I, Altman DG, McHaffie H, Owens N, Cooke RWI. Data sharing among data monitoring committees and responsibilities to patients and science. Trials 2013;14(102).

Kind regards,

Kylie

KYLIE HUNTER | Systematic Reviews Project Officer

NHMRC Clinical Trials Centre

THE UNIVERSITY OF SYDNEY

L6 Medical Foundation Building | 92-94 Parramatta Rd | Camperdown | NSW | 2050

T +61 2 9562 5031 | F +61 2 9565 1863

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Blansfield, Earl (NIH/NICHD) [E]

From: Michael Carome <mcarome@citizen.org>
Sent: Wednesday, May 29, 2013 7:39 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]
Cc: Sidney Wolfe; Collins, Francis (NIH/OD) [E]
Subject: Neonatal Research Network SUPPORT Study Talking Points for Parents
Attachments: Neonatal Research Network_SUPPORT Study Talking Points.docx

Dear Alan and Kathy,

The attached document entitled "Neonatal Research Network SUPPORT Study: Talking Points for Parents" — which is publicly available on the website for the University of Texas Medical School at Houston at http://ped1.med.uth.tmc.edu/neo/SUPPORT%20info.html" — recently came to our attention. A review of this document reveals the continued dissemination of misleading information to parents of SUPPORT study subjects, a process that began when consent was first sought from these parents. Furthermore, the document contains statements that could easily be shown to be false.

We hope you can respond to the following questions regarding this document:

(1) Did NIH play a role in the development or review of these talking points for parents?
(2) Was this document distributed to all institutions involved in the conduct of the SUPPORT study?
(3) Does NIH agree with the entire content of the document?
(4) Had you seen this document prior to our sending it to you? If so, what was your response to it?

We look forward to your responses.

Sincerely,

Michael A. Carome, M.D.
Deputy Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

http://ped1.med.uth.tmc.edu/neo/SUPPORT%20info.html

Neonatal Research Network SUPPORT Study

Talking Points for Parents

- Yes, we're aware of what's been said in the press.
- The early articles, including the first one in the New York Times, had many factual errors. The reporters were quoting from websites. They made no attempt to speak with people involved with the study or other experts in the field.
- The more recent articles present a more balanced view because they talked with people who really knew about the study. Those experts believe that it was an important study and that it was carefully done and that the information provided to parents was appropriate.
- No one has criticized the study itself (the need for it, the way it was done, the importance of the findings). The issue is what was or wasn't in the consent form used in study.
- We and the other people who participated in this study, explained the study and the risks to the families as best we could, based on what we knew at the time.

Information for Staff Who Talk with Parents

The doctors and nurses who do studies in the Neonatal Research Network are dedicated to improving the care and outcomes of newborn infants by comparing current care practices with potentially better practices. We are indebted to our patients and their parents who allow them to participate in research studies, and we do our best to inform parents of the risks that are known at the time new studies are started. It is unfortunate that the controversy surrounding the consent process for the SUPPORT trial could affect our patients and their families and their trust in us.

Why was the study done?

When the SUPPORT study was planned in 2002, there was limited evidence from studies done in the 1950s, that excessive levels of inhaled oxygen in premature infants increased the risk of retinopathy of prematurity (ROP, a common eye problem in premature infants) and that severe restriction of oxygen, without measuring the oxygen level in the blood, increased the risk of death. These old studies were done when it was impossible to measure the level of oxygen in the baby's bloodstream. When the SUPPORT study was planned, oxygen levels could be continuously monitored with skin sensors. There had never been a study to find the optimal goal for blood oxygen levels in very premature babies right after birth.

The American Academy of Pediatrics (AAP) recommended that the oxygen level be kept between 85 and 95% as much as possible in premature babies. The SUPPORT study compared using oxygen saturation targets toward the lower and upper ends of the recommended range: 85-89% compared with 91-95%.

What risks were disclosed to study participants?

When the babies were enrolled, it was clearly explained to the parents that the purpose of the study was to see which oxygen saturation target range best limited the risk of ROP. The criticism of the consent paperwork is that ROP was not mentioned again in the "Risks and Benefits" section.

There was also a criticism that death should have been disclosed as a risk for babies in the study. Before this study was completed, there was no evidence that mortality might be increased in either of the oxygen ranges studied. Indeed, babies enrolled in the trial had lower mortality and the same risk of blindness as similarly premature babies who were not enrolled in the study.

The overall risks of severe ROP, blindness, and death were not increased by participation in the SUPPORT study (as compared to not being in the study). The babies in the lower oxygen saturation target group (as compared to babies in the higher saturation target group) had lower risk of severe ROP but higher risk of death and no difference in blindness. This is vitally important information that was badly needed to help neonatologists and parents decide the best target range to use for their very premature patients.

Were the patients in the SUPPORT trial adequately protected as research subjects?

We believe that these babies and their parents were fully protected using every available practice for protecting subjects. The study was conducted with the ongoing supervision of an independent Data Safety and Monitoring Committee that reviewed study findings monthly. Each center had annual reviews of the protocol by their IRBs who were fully provided with the results of the Safety Board's findings. All enrolled infants were followed to 2 years of age with full assessments of health, vision and learning. At 2 years, despite the difference in retinopathy at the time of hospital discharge, the number of infants with blindness was equal in both arms. In addition, there were no differences in the intellecual outcomes between the two groups.

Has the SUPPORT trial improved care for tiny babies?

Before this study was completed, doctors and nurses caring for premature babies had no good information about what oxygen levels were best. We now have a much better understanding of the advantages and disadvantages of different oxygen levels in these babies. There are 3 other similar studies that have not been completed. If all these studies show the same thing, they will change practice and save the lives of 1000s of babies each year.

From: Finer, Neil
To: William Tarnow-Mordi; Wally Carlo, M.D.
Cc: Darlow Brian; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: an open letter to OHRP about SUPPORT
Date: Wednesday, May 29, 2013 1:04:52 AM

Thanks for sending this
Be well
Neil

-----Original Message-----
From: William Tarnow-Mordi [mailto:williamtm@med.usyd.edu.au]
Sent: Wednesday, May 29, 2013 4:54 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Darlow Brian; Rosemary Higgins
Subject: Fwd: an open letter to OHRP about SUPPORT

Dear Wally and Neil

Brian Darlow and I have accepted an invitation to co-sign a letter from a group of over 20 bioethics leaders and academics with experience in human subjects research to Jerry Menikoff, Director of OHRP.

The letter urges OHRP to reconsider their findings that the institutions involved with the SUPPORT trial failed to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks of enrollment in the study and it asserts that this conclusion was a substantive error that will have adverse implications for future research.

A copy with the original email invitation is attached.

best wishes

William
--
William Tarnow-Mordi
Professor of Neonatal Medicine, Westmead Hospital NHMRC Clinical Trials Centre, University of Sydney, Foundation Director Westmead International Network for Neonatal Education and Research WINNER Centre - working together to win healthy survival.

From: Finer, Neil
To: Luc Brion; Gantz, Marie; Wrage, Lisa Ann
Cc: Das, Abhik; doctorlevan@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll; Pablo Sanchez; Wally Carlo, M.D.
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT
Date: Wednesday, May 29, 2013 12:57:46 AM

This reads well, the message is clear and the discussion is brief
Nice job!!
Neil

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Sunday, May 26, 2013 1:22 PM
To: Gantz, Marie; Wrage, Lisa Ann
Cc: Das, Abhik; doctorlevan@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne; Finer, Neil; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll; Pablo Sanchez; Wally Carlo, M.D.
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT

Thanks for all the comments.
I attach a revised version, in which I tried to respond to all the suggestions I have received so far.
Lisa; in the tables: is the number in parenthesis after the median the quartile range?
We will of course need to decide if we want to conduct a survey of practices.
Thanks
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
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luc.brion@utsouthwestern.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, May 24, 2013 2:27 PM
To: Wrage, Lisa Ann; Luc Brion
Cc: Das, Abhik
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT

I agree that running the models with and without BW and/or GA and looking at the effect on the other covariates to see if any changes make sense or not is a good way of assessing whether both can be used in the model.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-547-5110

From: Wrage, Lisa Ann
Sent: Friday, May 24, 2013 3:10 PM
To: 'Luc Brion'
Cc: Gantz, Marie; Das, Abhik
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT

Hi Luc,
There was a concern expressed about possible collinearity between BW and GA in our models. In 6 of our 7 models both BW and GA are highly significant, so at least to me this is one indication that the correlation between BW and GA are not causing a problem in these models. The one exception is for secondary outcome BPD, in this model GA is not statistically significant and BW is. What I could do is run this model excluding one or the other and see if it makes a difference in the result. Marie may have other ideas, I am not sure that it is necessary to do a lot of other analysis to determine if BW and GA are causing any problems in the models.
I also have a note in one table that I need to review a definition (epinephrine in DR), since you are including that in the paper I need to go ahead and review that before you submit.
I will do these things next week.
Let me know if there's something else that you are aware you need from me.
Hope you have a great weekend!
Thanks,
Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, May 23, 2013 10:33 PM
To: Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Myra Wyckoff; Roy Heyne; Mambarambath Jaleel; M.D." <WCarlo@peds.uab.edu>, "'; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; archerst@mail.nih.gov
Subject: Jackie LeVan Manuscript on Changes after SUPPORT

Here is the manuscript I sent you on April 7 for comments.
Please let me know if this manuscript is ready to be submitted.

Rose and Stephanie:

Please let me know what boiler plate should be used, or if there is any process I should follow

Thanks

Luc

Luc P. Brion, MD
Professor of Pediatrics
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The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Wally Carlo, M.D.
To: William Tarnow-Mordi; Neil Finer
Cc: Darlow Brian; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: an open letter to OHRP about SUPPORT
Date: Tuesday, May 28, 2013 11:26:09 PM

Dear William.

Thanks for sharing. I have been in contact with Ben about related efforts.

Wally

-----Original message-----

From: William Tarnow-Mordi <williamtm@med.usyd.edu.au>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, Neil Finer <nfiner@ucsd.edu>
Cc: Darlow Brian <brian.darlow@otago.ac.nz>, Rosemary Higgins <higginsr@mail.nih.gov>
Sent: Wed, May 29, 2013 02:54:42 GMT+00:00
Subject: Fwd: an open letter to OHRP about SUPPORT

Dear Wally and Neil

Brian Darlow and I have accepted an invitation to co-sign a letter from a group of over 20 bioethics leaders and academics with experience in human subjects research to Jerry Menikoff, Director of OHRP.

The letter urges OHRP to reconsider their findings that the institutions involved with the SUPPORT trial failed to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks of enrollment in the study and it asserts that this conclusion was a substantive error that will have adverse implications for future research.

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best wishes

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Professor of Neonatal Medicine, Westmead Hospital
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Foundation Director
Westmead International Network for Neonatal Education and Research
WINNER Centre - working together to win healthy survival.

Blansfield, Earl (NIH/NICHD) [E]

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, May 28, 2013 10:14 PM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: upshot of this afternoon's meeting at HHS
Attachments: NEJM HudsonP-dm1 klh fsc ag fsc again 5-28-13.docx

Hi all,

That was quite a meeting at HHS this afternoon.

Bottom line (because it's late, this is a bit sketchy, more details available on request):

(b)(5)

That's it from here.

FC

Page 1106 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1107 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1108 of 2000

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Page 1109 of 2000

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Page 1110 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1111 of 2000

Withheld pursuant to exemption

(b)(5)

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From:	Luc Brion
To:	Gantz, Marie; Wrage, Lisa Ann; Das, Abhik; doctorlevan@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne; nfiner@ucsd.edu; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll; Pablo Sanchez; Wally Carlo, M.D.
Subject:	FW: Jackie LeVan Manuscript on Changes after SUPPORT
Date:	Tuesday, May 28, 2013 3:14:12 PM
Attachments:	Jackie Manuscript NRN 052613 LPB.doc Authorship Responsibility.PDF

Could you please complete and sign the attached authorship responsibility form and email it to me.
Thanks a lot
Luc

From: Luc Brion
Sent: Sunday, May 26, 2013 6:22 AM
To: Gantz, Marie; Wrage, Lisa Ann
Cc: Das, Abhik; doctorlevan@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne; nfiner@ucsd.edu; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll; Pablo Sanchez; Wally Carlo, M.D.
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT

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Lisa; in the tables: is the number in parenthesis after the median the quartile range?
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luc.brion@utsouthwestern.edu

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Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

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To: Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Myra Wyckoff; Roy Heyne; Mambarambath Jaleel; M.D." <WCarlo@peds.uab.edu>, "'; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; archerst@mail.nih.gov
Subject: Jackie LeVan Manuscript on Changes after SUPPORT

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luc.brion@utsouthwestern.edu

CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Changes associated with SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: ~~not applicable~~ NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Formatted: Font: (Default) Times New Roman

What's known on This Subject: The NICHD SUPPORT trial showed that continuous positive airway pressure is an alternative to endotracheal intubation for delivery room therapy in very preterm infants.

What This Study Adds: The proportion of endotracheal intubation significantly decreased after the SUPPORT trial in NICHD centers that participated in the SUPPORT

Revised 5/26~~7~~/13 ~~3 PM~~

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 231 words
Article length: 2,191~~059~~ words

Abstract

Introduction
In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare care process and outcomes before SUPPORT and after its publication.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one. The proportion of DR intubation decreased only in centers with >=80% DR intubation prior to SUPPORT.

Discussion:
This study is limited by its observational before/after design.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ths weeks to $27^{6/7}$ths weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within one hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in May~~June~~ 2010. The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of the current study was to determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal

intubation in the DR in preterm inborn infants. We hypothesized that publication of SUPPORT would be followed by a decrease in proportion of intubation in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We hypothesized that the decrease in proportion of intubation in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. We also aimed to determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks, including risk of death or BPD (defined by oxygen use at 36 weeks of postmenstrual age (PMA)), death or severe ROP (defined as ROP surgery or retinal detachment) at the time of discharge and death before discharge. We also hypothesized that publication of SUPPORT would not affect the risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP (defined as ROP surgery or retinal detachment), and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second birth cohort of patients starting after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those in the SUPPORT trial. Eligible infants were inborn at $24^{0/7}$th to $27^{6/7}$th weeks at birth by best obstetrical estimate, without known malformations, delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study span of the study (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. We included patients who died early, but excluded patients whose support was either withheld or withdrawn.

Baseline variables

Neonatal and maternal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were the intubation in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP

surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Secondary outcome variables:

Secondary outcomes of interest included BPD, severe ROP and other ROP outcomes, deaths within 12 hours or by 36 weeks PMA, surfactant use, DR outcomes, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and Student t-tests or Wilcoxon tests, as appropriate, for continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. These models included pre-specified prenatal covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted

tests, and that preceded the outcome. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes. We created a model specific for BPD, considering the following potential covariates: intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch. Additionally, the Cochran-Mantel-Haenszel test was used to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations $\geq$ 80% (based on pre-SUPPORT proportion at Parkland, an NRN center which did not participate in the Feasibility Trial)[17] and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

Results

There were a total of 6,601 infants born at $24^{0/7}$ to $27^{6/7}$ weeks gestational age during 2003-2004 (n=2,998) or 2010- 2012 (n=3,603) and included in the GDB (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361

were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants. Of these 1,617 infants were in the pre-SUPPORT group and 2,232 infants were in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.001), maternal hypertension (27.4% vs. 19.9%, p<0.001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed- a significant decrease in the proportion of DR intubation and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99),- severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89),, and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2).

Secondary outcomes are shown in Tables 3 and 4. -The adjusted risks of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risks of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly

different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the delivery room during the first and second epochs in the 11 centers in the study. The correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.17). Centers were also combined into two groups: two centers with pre-SUPPORT percent DR intubations < 80% and nine centers with pre-SUPPORT percent DR intubations ≥ 80%. -The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks gestational age born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR intubation and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR intubation decreased significantly only in centers with a high baseline proportion. There were also significant decreases in risk of severe ROP and death or mechanical ventilation at day of life 7 in the group of infants in the post-SUPPORT group. These findings contrast with a previous study of the NICHD NRN,

which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002.[18] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population and secular trends. Since this study ~~proposal~~ includes several outcome variables, it is likely that some differences ~~will~~ reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP after ROP reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies ~~besides the SUPPORT trial~~, e.g., studies on antenatal steroids,[19] treatment and prophylaxis of patent ductus

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arteriosus,[20-22] synchronized nasal intermittent positive-pressure ventilation,[23] prevention of central line-associated bloodstream infections,[24,25] or nutrition.[26] Delivery room practice, including oxygen exposure and administration of epinephrine, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[27]

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Conclusion

After adjustment for baseline variables, the risks of DR intubation, ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT results. The adjusted risks of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risks of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after SUPPORT. -These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
(Maternal??)Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room epinephrine **	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min.	4.4 (2.5)	3.9 (2.4)	<0.0001
Apgar score, 5 min.	6.5 (2.0)	6.3 (2.2)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	13 (0.8)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure or nasal intermittent positive-pressure ventilation (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

[1] presented as ~~mean (SD),~~ median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge ,and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate
[4] survivors to discharge or 120 days, whichever came first, max is 120 days.
**Lisa needs to take a closer look at this definition before finalized

Figure 1

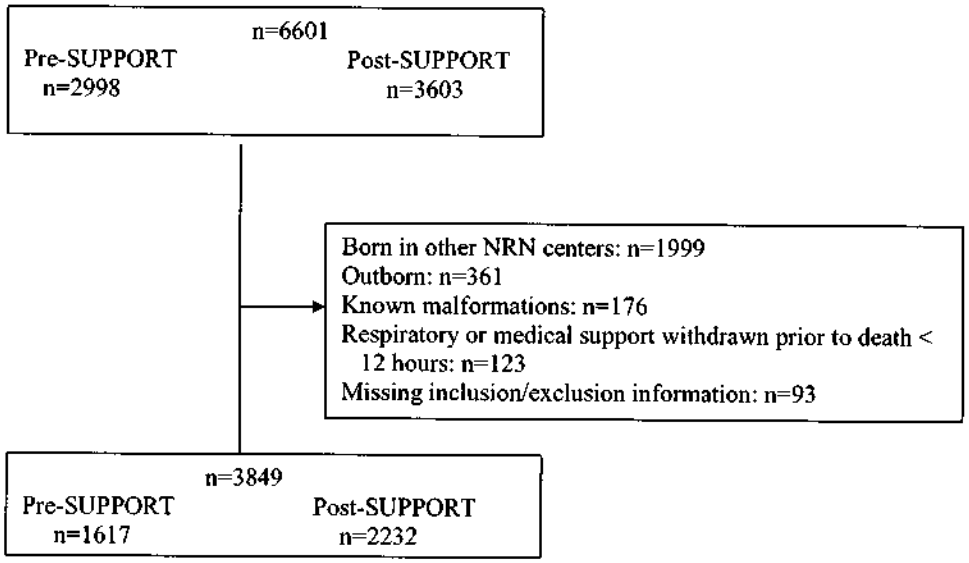
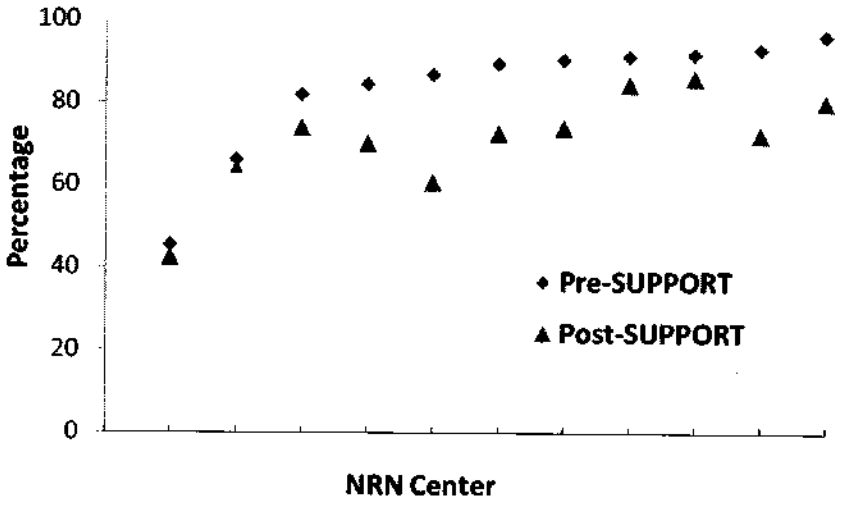


Figure 2



NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

Title of manuscript _____
First author _____

☐ A. I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. I agree to allow the corresponding author to serve as the primary correspondent with the journal editorial office, to review the edited typescript and proof.

☐ B. I have read and given final approval of the submitted manuscript.

C. To qualify for authorship, you must check at least 1 box for each of the 3 categories of contributions listed below.

I have made substantial contributions to the intellectual content of the paper as described below.

1. (check at least 1 of the 3 below)

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   ☐ acquisition of data
   ☐ analysis and interpretation of data

2. (check at least 1 of 2 below)

   ☐ drafting of the manuscript
   ☐ critical revision of the manuscript for important intellectual content

3. (check at least 1 below)

   ☐ statistical analysis
   ☐ obtaining funding
   ☐ administrative, technical, or material support
   ☐ supervision
   ☐ no additional contributions
   ☐ other (specify)
   ☐ or are disclosed in an attachment.

Your Signature _____ Date Signed _____

From: Karen Osborne RN
To: Roger Faix; Bradley Yoder; Ed Clark; Jacquie Bernard; John Stillman; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT follow-up - PHI
Date: Tuesday, May 28, 2013 11:59:27 AM
Attachments: securedoc_20130528T155923.html

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THE UNIVERSITY OF UTAH

May 28, 2013
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From: Karen Osborne RN <Karen.Osborne@hsc.utah.edu>
To: higginsr@mail.nih.gov
Subject: **RE: SUPPORT follow-up - PHI**
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Luc Brion"; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial
Date: Tuesday, May 28, 2013 10:50:00 AM

Yes – have them fill out the authorship forms prior to publications subcommittee review
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, May 28, 2013 10:49 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Rose:
I have sent the manuscript to all authors.
Should I send them the NRN Authorship document now or after Lisa and Marie have finalized the statistics?
Luc

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, May 28, 2013 7:37 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Luc Brion
Subject: RE: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Have all the GDB co-authors seen and approved it?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, May 28, 2013 8:37 AM
To: 'Luc Brion'; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Publication | LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Rose,

Does Luc need to do anything else with Dr. LeVan's revised analysis plan other than work with Marie to complete it for the paper?

Stephanie

Stephanie Wilson Archer
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, May 23, 2013 10:26 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: revised protocol

Stephanie;
Please let me know what I need to do to get this going forward.
Thanks
Luc

Luc P. Brion, MD
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From: Luc Brion
Sent: Wednesday, May 15, 2013 8:29 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: revised protocol

You are right; she did present a portion of what was planned in the protocol.
This is just a revision to match what was done so far and match what everyone has decided (Marie, Wally, etc).
Luc

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From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Wednesday, May 15, 2013 8:20 AM
To: Luc Brion
Cc: Meg Cunningham (mcunningham@rti.org)
Subject: RE: revised protocol

Hi Luc,

I thought that Dr. LeVan presented her abstract at PAS this month. Can you tell me if her proposal is just a revision of what will be analyzed for the manuscript or a brand new PAS Abstract?

Thanks,

Stephanie

Stephanie Wilson Archer
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, May 13, 2013 10:29 PM
To: Archer, Stephanie (NIH/NICHD) [E]; 'mcunningham@rti.org'
Subject: Fw: revised protocol

For PAS 2014
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, May 13, 2013 06:18 PM
To: (b)(6)@gmail.com; (b)(6)gmail.com>; Wrage, Lisa Ann <wrage@rti.org>; Gantz, Marie <mgantz@rti.org>; Myra Wyckoff <Myra.Wyckoff@UTSouthwestern.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Roy Heyne <Roy.Heyne@UTSouthwestern.edu>; Mambarambath Jaleel <Mambarambath.Jaleel@UTSouthwestern.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; Das, Abhik <adas@rti.org>; Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion <Luc.Brion@UTSouthwestern.edu>
Subject: revised protocol

Roy suggested to include the 2011 GDB information in the sample size calculation.
The number is almost identical to the 2010 GDB data.
Here is a revised version of the protocol including the 2011 data (page 11).
Best regards,
Luc

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luc.brion@utsouthwestern.edu

Blansfield, Earl (NIH/NICHD) [E]

From: Lantos, John <jlantos@cmh.edu>
Sent: Tuesday, May 28, 2013 7:13 AM
To: wlm1@uchicago.edu; brian.darlow@otago.ac.nz; keith.barrington@umontreal.ca; williamtm@med.usyd.edu.au; askie@ctc.usyd.edu.au
Subject: an open letter to OHRP about SUPPORT
Attachments: SUPPORT5 .6.pdf

Friends,

A group of folks in the US, mostly bioethicists, some pediatricians, have written a letter to OHRP. It was, as you might imagine, a long process to get some consensus about language among this feisty group. We've finally agreed about what the letter should say.

We want to send it tomorrow afternoon. We are hoping that either the NEJM or JAMA will agree to run it as an ePub before print this week.

I'm writing to ask if you are interested in adding your names to the list of people who have signed it. We have decided not to have anyone who was directly involved in SUPPORT and so have very few neonatologists on the list.

If you are interested, send me a note, and let me know how you'd like your title and affiliation to be listed. You could ask others, too, if you'd like.

Note: at this point, we cannot change the letter, because this is what went out and what - after long discussions - people have agreed to sign on to.

John
John D. Lantos M.D.
816-701-5284

ASSOCIATION OF bioethics PROGRAM DIRECTORS

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May 27, 2013

Jerry Meniko , M.D., J.D.
Director
O ce for Human Research Protec ons
Department of Health and Human Services
Suite 200
1101 Woo on Parkway
Rockville, MD 20852

Dear Dr Meniko ,

We are a group of scholars and leaders in bioethics with extensive experience in ethical and regulatory issues in pediatrics and human subjects research. We urge you to reconsider OHRP's nding that the ins tu ons involved with the Surfactant, Posi ve Pressure, Oxygena on Randomized Trial (SUPPORT) failed to meet regulatory informed consent requirements, in par cular regarding reasonably foreseeable risks of enrollment in the study. We believe this conclusion was a substan ve error that will have adverse implica ons for future research.

SUPPORT was undertaken because there was no reliable scien c evidence as to which blood oxygen satura on levels were op mum for extremely premature babies. The infants in the study were randomized to oxygen satura on targets that were consistent with standard clinical care at the participating institutions. OHRP's conclusion that the study's experimental evalua on of these otherwise rou nely used oxygen satura on levels exposed subjects to addi onal risk (above the risks of rou ne clinical treatment) is not supported by evidence.

Furthermore, OHRP's conclusion that the SUPPORT investigators violated federal regula ons in failing to include speci c informa on elements in the parental permission documents regarding risks of the study interven ons is without substan ve merit. While the permission forms conceivably could have been improved, the risks of re nopathy of prematurity and death during par cipa on in this factorial design study were noted. There is nothing to indicate that the ins tu onal bodies responsible for reviewing the SUPPORT study failed to exercise appropriate care and judgment as to all the factors required by the Common Rule in approving the study. OHRP should not sanc on research ins tu ons simply because it disagrees with their assessment of the risks of research, absent a nding that an ins tu on has failed to meet the terms of its federal-wide assurance, such as in the manner in which its IRB is cons tuted or

operates. Accordingly, a nding by OHRP that the ins tu ons conduc ng the SUPPORT study failed to meet applicable regulatory requirements, when unsupported by substan al evidence, would be arbitrary and capricious.

In the absence of a formal mechanism for appeal, we urge you to regard this expression of disagreement by signatories represen ng leaders in research ethics as an appropriate basis for OHRP to reconsider this decision. Allowing the decision to stand would be unfair to the inves gators and ins tu ons involved in SUPPORT. It would also set a precedent that will impede ongoing and future pa ent-centered outcomes studies. Such studies are crucial to advance medical prac ce, reduce risks, improve outcomes, and enhance cost e ec veness, par cularly in pediatrics.

The consent process for clinical research can no doubt be improved. The recent scru ny of SUPPORT highlights the challenges faced in clinical research. We believe that these challenges can best be addressed through open discussions among the full range of relevant stakeholders. We stand ready to par cipate in any such discussions to assist OHRP and the Department in their e orts to assure the highest standards of ethics in research.

Sincerely,

Benjamin Wilfond, MD, Professor of Pediatrics, University of Washington; Director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

David Magnus, PhD, Thomas A. Ra n Professor of Medicine and Biomedical Ethics and Professor of Pediatrics, Director, Center for Biomedical Ethics, Stanford University*

Armand Antomarria, MD, PhD, Associate Professor of Pediatrics, University of Cincinna ; Director, Ethics Center, Cincinna Children's Hospital Medical Center*

Paul Appelbaum, PhD, Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law, Columbia University

Renee D. Boss, MD, MHS, Division of Neonatology, Department of Pediatrics, Johns Hopkins School of Medicine; Johns Hopkins Berman Ins tute of Bioethics

Arthur L. Caplan, PhD, Drs. William F. and Virginia Connolly Mi y Chair, Director, Division of Medical Ethics, New York University Langone Medical Center

Alexander M. Capron, University Professor, Sco H. Bice Chair in Healthcare Law, Policy and Ethics, Co-Director, Paci c Center for Health Policy and Ethics, University of Southern California

Ellen Wright Clayton, MD, JD, Professor of Law, Vanderbilt Law School; Craig-Weaver Professor of Pediatrics, Vanderbilt University School of Medicine

Mildred Cho, PhD, Professor of Pediatrics, Stanford University; Associate Director, Stanford Center for Biomedical Ethics, Stanford University*

Douglas Diekema, MD MPH, Professor of Pediatrics, University of Washington; Director of Education, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute

Joel Frader MD MA, Professor of Pediatrics and Medical Humani es & Bioethics, Northwestern University

Ruth R. Faden, PhD, MPH, Philip Franklin Wagley Professor of Biomedical Ethics; Director, Johns Hopkins Berman Ins tute of Bioethics

Chris Feudtner, MD, PhD, Associate Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania; Steven D. Handler Endowed Chair of Medical Ethics, Director Department of Medical Ethics, Children's Hospital of Philadelphia

Joseph J. Fins, MD, E. William Davis, Jr., MD Professor of Medical Ethics, Chief, Division of Medical Ethics, Professor of Medicine, Weill Medical College of Cornell University and Director of Medical Ethics, New York Presbyterian Hospital-Weill Cornell Medical Center

Norman Fost, MD, MPH, Professor, Pediatrics and Bioethics, University of Wisconsin School of Medicine and Public Health

D. Micah Hester, PhD, Chief, Division of Medical Humani es, University of Arkansas for Medical Sciences; Clinical Ethicist, Arkansas Children's Hospital

Steven Jo e, MD, MPH, Associate Professor of Pediatrics, Global Health and Social Medicine, Harvard Medical School; Hospital Ethicist, Dana-Farber Cancer Ins tute

Je rey Kahn, PhD, MPH, Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy, Deputy Director for Policy and Administra on, Johns Hopkins Berman Ins tute of Bioethics

Nancy E. Kass, ScD, Phoebe R. Berman Professor of Bioethics and Public Health, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Deputy Director for Public Health, Johns Hopkins Berman Ins tute of Bioethics

Eric Kodish MD, FJ O'Neill Professor and Chair, Department of Bioethics, Professor of Pediatrics, Lerner College of Medicine, Cleveland Clinic

John D. Lantos MD, Professor of Pediatrics, University of Missouri at Kansas City; Director, Children's Mercy Hospital Bioethics Center

Laurence McCullough , PhD, Dalton Tomlin Chair in Medical Ethics and Health Policy, Professor of Medicine and Medical Ethics; Associate Director for Educa on, Center for Medical Ethics and Health Policy, Baylor College of Medicine

Ross McKinney, Jr., MD, Professor of Pediatric Infec ous Diseases; Director, Trent Center for Bioethics, Humani es and History of Medicine, Duke University and School of Medicine

P. Pearl O'Rourke, MD, Director, Human Research A airs, Partners HealthCare

Kathleen E. Powderly, CNM, PhD, Director, John Conley Division of Medical Ethics and Humani es, SUNY Downstate Medical Center

Lainie Friedman Ross, MD, PhD, Carolyn and Ma hew Bucksbaum Professor of Clinical Ethics, Professor, Departments of Pediatrics, Medicine, and Surgery, Co-Director, Ins tute for

Transla onal Medicine, Associate Director, MacLean Center for Clinical Medical Ethics, University of Chicago*

Richard Sharp, PhD Director of Research Center for Ethics, Humani es and Spiritual Care, Cleveland Clinic

Sadath Sayeed, MD, JD, Assistant Professor of Global Health and Social Medicine, Harvard University

Jeremy Sugarman, MD, MPH, MA, Harvey M. Meyerho Professor of Bioethics and Medicine, Deputy Director for Medicine, Johns Hopkins Berman Ins tute of Bioethics

Tom Tomlinson, PhD, Director, Center for Ethics and Humani es in the Life Sciences, College of Human Medicine, Michigan State University

Robert D. Truog, MD, Professor of Medical Ethics, Anesthesiology, & Pediatrics, Director of Clinical Ethics, Harvard Medical School; Senior Associate in Critical Care Medicine, Children's Hospital Boston

Yoram T. Unguru, MD, MS, MA, Division of Pediatric Hematology/Oncology, The Herman and Walter Samuelson Children's Hospital at Sinai; Johns Hopkins Berman Ins tute of Bioethics

Kathryn L. Weise, MD, MA, Program Director, Cleveland Fellowship in Advanced Bioethics, Department of Bioethics, Cleveland Clinic

Stuart Youngner, MD, Professor of Psychiatry and Cogni ve Science, Susan E. Watson Professor of Bioethics, Chair, Department of Bioethics, Case Western Reserve University*

[**individuals who work at the same institutions as the SUPPORT investigators*]

cc:

The Honorable Kathleen Sibelius, Secretary, Department of Health and Human Services (HHS)

The Honorable Howard K. Koh, Assistant Secretary for Health, HHS

Dr. Francis Collins, Director, Na onal Ins tutes of Health

Dr. Alan E. Gu macher, Director, Eunice Kennedy Shriver Na onal Ins tute of Child Health and Development

Dr. Christopher Aus n, Director, Na onal Center for Advancing Clinical and Transla onal Sciences

Dr Richard B. Marchase, Vice President, Research, University of Alabama at Birmingham

Dr Je rey R Botkin, Chair, Secretary's Advisory Commi ee on Human Research Protec ons

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, May 27, 2013 5:41 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: support f/u with hhs
Attachments: Proposed Action Steps for the Secretary 5-26-13 klh fsc.docx

FC
I think sending this to Bill is a good idea.
Your edits look great. I accepted all of them (including the annoying grammarian one!). Clean version attached.
Klh

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, May 27, 2013 3:46 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: support f/u with hhs

Hi Kathy,

See my suggested edits on the mostly excellent f/u proposals. I have rearranged things slightly to indicate that the (b)(5) – I assume that was your intention?

If we four are OK with this, shall I transmit to Bill in advance of tomorrow's meeting?

FC

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 26, 2013 3:35 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: support f/u with hhs

Here are some ideas for HHS for Tuesday meeting.
I will let Jeff know where we are and ask about how much flexibility he has.
A key upcoming date is June 6 which is date of NICHD council. (b)(5)

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

From: Luc Brion
To: Gantz, Marie; Wrage, Lisa Ann
Cc: Das, Abhik; doctorlevan@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; Roy Heyne; nfiner@ucsd.edu; Myra Wyckoff; Mambarambath Jaleel; Barbara Stoll; Pablo Sanchez; Wally Carlo, M.D.
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT
Date: Sunday, May 26, 2013 7:22:11 AM
Attachments: Jackie Manuscript NRN 052613 LPB.doc

Thanks for all the comments.
I attach a revised version, in which I tried to respond to all the suggestions I have received so far.
Lisa; in the tables: is the number in parenthesis after the median the quartile range?
We will of course need to decide if we want to conduct a survey of practices.
Thanks
Luc

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Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern Medical Center at Dallas
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Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, May 24, 2013 2:27 PM
To: Wrage, Lisa Ann; Luc Brion
Cc: Das, Abhik
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT

I agree that running the models with and without BW and/or GA and looking at the effect on the other covariates to see if any changes make sense or not is a good way of assessing whether both can be used in the model.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Wrage, Lisa Ann
Sent: Friday, May 24, 2013 3:10 PM
To: 'Luc Brion'
Cc: Gantz, Marie; Das, Abhik
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT

Hi Luc,
There was a concern expressed about possible collinearity between BW and GA in our models. In 6 of our 7 models both BW and GA are highly significant, so at least to me this is one indication that the correlation between BW and GA are not causing a problem in these models. The one exception is for secondary outcome BPD, in this model GA is not statistically significant and BW is. What I could do is run this model excluding one or the other and see if it makes a difference in the result. Marie may have other ideas, I am not sure that it is necessary to do a lot of other analysis to determine if BW and GA are causing any problems in the models.
I also have a note in one table that I need to review a definition (epinephrine in DR), since you are including that in the paper I need to go ahead and review that before you submit.
I will do these things next week.
Let me know if there's something else that you are aware you need from me.
Hope you have a great weekend!
Thanks,
Lisa

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, May 23, 2013 10:33 PM
To: Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Myra Wyckoff; Roy Heyne; Mambarambath Jaleel; M.D." <WCarlo@peds.uab.edu>, "'; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; archerst@mail.nih.gov
Subject: Jackie LeVan Manuscript on Changes after SUPPORT

Here is the manuscript I sent you on April 7 for comments.
Please let me know if this manuscript is ready to be submitted.

Rose and Stephanie:
Please let me know what boiler plate should be used, or if there is any process I should follow
Thanks
Luc

Luc P. Brion, MD
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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Changes associated with SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: ~~not applicable~~ NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Formatted: Font: (Default) Times New Roman

What's known on This Subject: The NICHD SUPPORT trial showed that continuous positive airway pressure is an alternative to endotracheal intubation for delivery room therapy in very preterm infants.

What This Study Adds: The proportion of endotracheal intubation significantly decreased after the SUPPORT trial in NICHD centers that participated in the SUPPORT

Revised 5/26~~7~~/13 ~~3 PM~~

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 231 words
Article length: 2,191~~059~~ words

Abstract

Introduction
In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare care process and outcomes before SUPPORT and after its publication.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one. The proportion of DR intubation decreased only in centers with >=80% DR intubation prior to SUPPORT.

Discussion:
This study is limited by its observational before/after design.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ths weeks to $27^{6/7}$ths weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within one hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in May~~June~~ 2010. The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of the current study was to determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal

intubation in the DR in preterm inborn infants. We hypothesized that publication of SUPPORT would be followed by a decrease in proportion of intubation in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We hypothesized that the decrease in proportion of intubation in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. We also aimed to determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks, including risk of death or BPD (defined by oxygen use at 36 weeks of postmenstrual age (PMA)), death or severe ROP (defined as ROP surgery or retinal detachment) at the time of discharge and death before discharge. We also hypothesized that publication of SUPPORT would not affect the risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP (defined as ROP surgery or retinal detachment), and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second birth cohort of patients starting after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those in the SUPPORT trial. Eligible infants were inborn at $24^{0/7}$th to $27^{6/7}$th weeks at birth by best obstetrical estimate, without known malformations, delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study span of the study (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. We included patients who died early, but excluded patients whose support was either withheld or withdrawn.

Baseline variables

Neonatal and maternal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were the intubation in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP

surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Secondary outcome variables:

Secondary outcomes of interest included BPD, severe ROP and other ROP outcomes, deaths within 12 hours or by 36 weeks PMA, surfactant use, DR outcomes, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and Student t-tests or Wilcoxon tests, as appropriate, for continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. These models included pre-specified prenatal covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted

tests, and that preceded the outcome. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes. We created a model specific for BPD, considering the following potential covariates: intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch. Additionally, the Cochran-Mantel-Haenszel test was used to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations ≥ 80% (based on pre-SUPPORT proportion at Parkland, an NRN center which did not participate in the Feasibility Trial)[17] and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

Results

There were a total of 6,601 infants born at $24^{0/7}$ to $27^{6/7}$ weeks gestational age during 2003-2004 (n=2,998) or 2010- 2012 (n=3,603) and included in the GDB (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361

were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants. Of these 1,617 infants were in the pre-SUPPORT group and 2,232 infants were in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.001), maternal hypertension (27.4% vs. 19.9%, p<0.001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed- a significant decrease in the proportion of DR intubation and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99),- severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89),, and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2).

Secondary outcomes are shown in Tables 3 and 4. -The adjusted risks of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risks of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly

different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the delivery room during the first and second epochs in the 11 centers in the study. The correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.17). Centers were also combined into two groups: two centers with pre-SUPPORT percent DR intubations < 80% and nine centers with pre-SUPPORT percent DR intubations ≥ 80%. -The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks gestational age born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR intubation and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR intubation decreased significantly only in centers with a high baseline proportion. There were also significant decreases in risk of severe ROP and death or mechanical ventilation at day of life 7 in the group of infants in the post-SUPPORT group. These findings contrast with a previous study of the NICHD NRN,

which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002.[18] These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

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The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population and secular trends. Since this study ~~proposal~~ includes several outcome variables, it is likely that some differences ~~will~~ reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. -It is possible that additional unknown biases or confounding variables could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP after ROP reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies ~~besides the SUPPORT trial~~, e.g., studies on antenatal steroids,[19] -treatment and prophylaxis of patent ductus

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arteriosus,[20-22] synchronized nasal intermittent positive-pressure ventilation,[23] prevention of central line-associated bloodstream infections,[24,25] or nutrition.[26] Delivery room practice, including oxygen exposure and administration of epinephrine, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.[27]

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Conclusion

After adjustment for baseline variables, the risks of DR intubation, ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT results. The adjusted risks of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risks of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after SUPPORT. -These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
(Maternal??)Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2] The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room epinephrine **	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min.	4.4 (2.5)	3.9 (2.4)	<0.0001
Apgar score, 5 min.	6.5 (2.0)	6.3 (2.2)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	13 (0.8)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure or nasal intermittent positive-pressure ventilation (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

[1] presented as ~~mean (SD),~~ median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge ,and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate
[4] survivors to discharge or 120 days, whichever came first, max is 120 days.
**Lisa needs to take a closer look at this definition before finalized

Figure 1

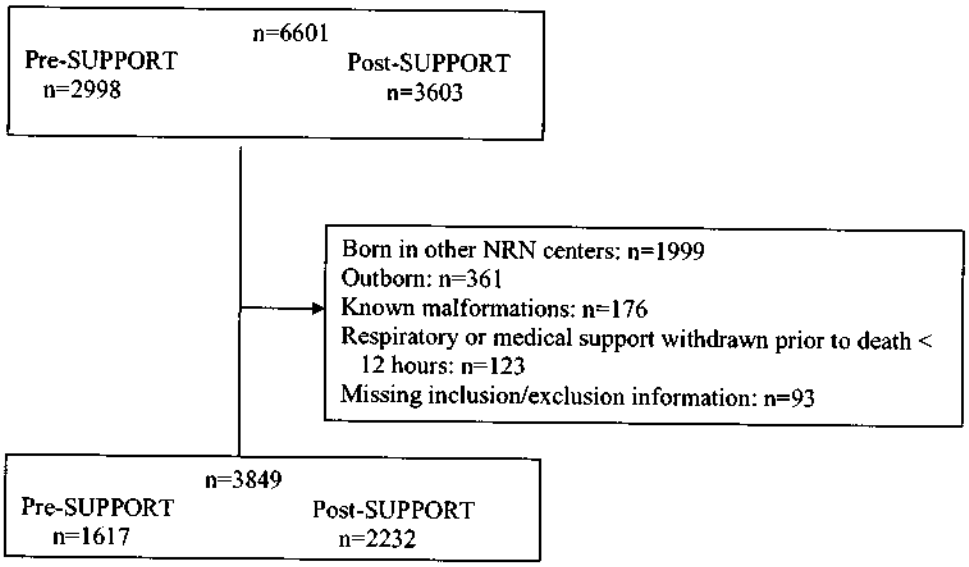
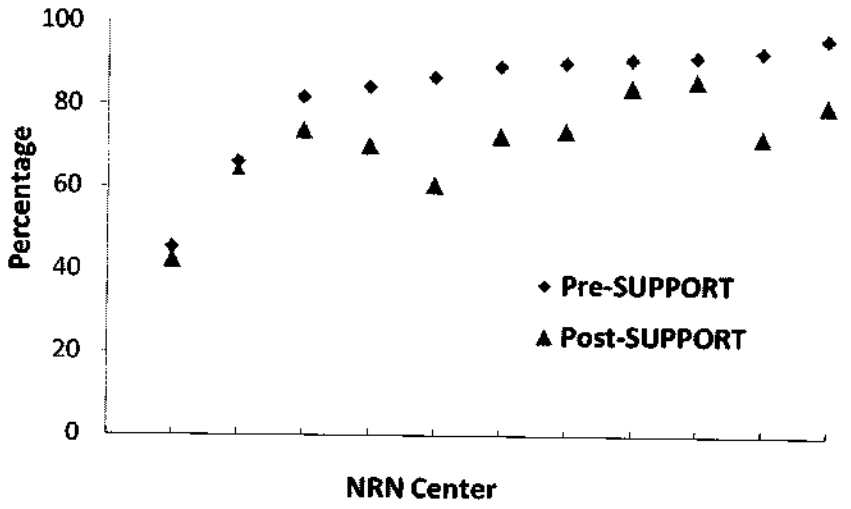


Figure 2



From: Luc Brion
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Jackie Manuscript NRN 050713 LPB
Date: Friday, May 24, 2013 9:05:30 PM

Rose
Thanks a lot.
I am not sure why the rate of late onset sepsis changed.
It may have nothing to do with SUPPORT; it is likely to be related to QIs on late onset sepsis or CLABSI.
The only way to find out would be to conduct a survey of practices in the NRN centers.
Neil asked another question about saturation.
Maybe we need to consider doing that. However I would be careful about making conclusions since all this is just observational, and surveys of centers only remotely reflect practice.
Luc

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 24, 2013 11:39 AM
To: Luc Brion
Subject: Jackie Manuscript NRN 050713 LPB

Luc-
A few comments – we have clincaltrials.gov registration numbers for both SUPPORT and GDB – I added them. Also – the rate of late onset sepsis has dramatically declined 40 to 23% - any thoughts??

Thanks
Rose

UT Southwestern Medical Center
The future of medicine, today.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bradley.yoder@hsc.utah.edu"; "Roger.Faix@hsc.utah.edu"; "Karen.Osborne@hsc.utah.edu"; "Ed.Clark@hsc.utah.edu"; "Jacquie.Bernard@hsc.utah.edu"; "John.Stillman@hsc.utah.edu"
Subject: Re: SUPPORT follow-up - PHI
Date: Friday, May 24, 2013 5:18:56 PM

Hi
I am unable to open.

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Friday, May 24, 2013 04:23 PM
To: Roger Faix <Roger.Faix@hsc.utah.edu>; Karen Osborne RN <Karen.Osborne@hsc.utah.edu>; Ed Clark <Ed.Clark@hsc.utah.edu>; Jacquie Bernard <Jacquie.Bernard@hsc.utah.edu>; John Stillman <John.Stillman@hsc.utah.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT follow-up - PHI

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Additional Help, click the following Help link.
Help - https://res.cisco.com/websafe/help?topic=RegEnvelope
About Cisco Registered Email Service - https://res.cisco.com/websafe/about

From: Luc Brion
To: Finer, Neil; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Myra Wyckoff; Roy Heyne; Mambarambath Jaleel; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Jackie LeVan Manuscript on Changes after SUPPORT
Date: Friday, May 24, 2013 3:19:10 PM

Thanks for your email and for your comments/suggestions.
When I asked previously about sending the survey about changes in practices that is included in the protocol, the answer I had received was not to send the survey now. Let's see what other authors think about this.
Lisa Wrage will run the analysis on epinephrine use in the DR.
Best regards,
Luc

From: Finer, Neil [nfiner@ucsd.edu]
Sent: Friday, May 24, 2013 8:28 AM
To: Luc Brion; Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Myra Wyckoff; Roy Heyne; Mambarambath Jaleel; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; archerst@mail.nih.gov
Subject: Re: Jackie LeVan Manuscript on Changes after SUPPORT

Hi Luc
With the benefit of hindsight and time I have a couple of questions – thoughts
Did you evaluate whether post SUPPORT units changed their SpO2 ranges and if so did you compare those that did with those that did not for ROP etc?
Did you look at the use of Epi in the DR – was there any change after SUPPORT?
Thanks for letting me see this again
I think this manuscript makes a unique point that has rarely (if ever) been shown with RCTs and is difficult enough to show with well done QA where it is is very hard to hold the gains
Be well
Neil

From: "Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>"
<Luc.Brion@UTSouthwestern.edu<mailto:Luc.Brion@UTSouthwestern.edu>>
Date: Thursday, May 23, 2013 7:33 PM
To: Lisa Wrage <wrage@rti.org<mailto:wrage@rti.org>>, Marie Gantz <mgantz@rti.org<mailto:mgantz@rti.org>>, Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>>, Myra Wyckoff <Myra.Wyckoff@UTSouthwestern.edu<mailto:Myra.Wyckoff@UTSouthwestern.edu>>, Roy Heyne <Roy.Heyne@UTSouthwestern.edu<mailto:Roy.Heyne@UTSouthwestern.edu>>, Mambarambath Jaleel <Mambarambath.Jaleel@UTSouthwestern.edu<mailto:Mambarambath.Jaleel@UTSouthwestern.edu>>, Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>, Abhik Das <adas@rti.org<mailto:adas@rti.org>>, Barbara Stoll <Barbara.Stoll@oz.ped.emory.edu<mailto:Barbara.Stoll@oz.ped.emory.edu>>, Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, Jackie LeVan (b)(6)@gmail.com<mailto:(b)(6)@gmail.com>>, Stephanie Archer <archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>>
Subject: Jackie LeVan Manuscript on Changes after SUPPORT

Here is the manuscript I sent you on April 7 for comments.
Please let me know if this manuscript is ready to be submitted.

Rose and Stephanie:
Please let me know what boiler plate should be used, or if there is any process I should follow
Thanks
Luc

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "(Luc.Brion@UTSouthwestern.edu)"
Subject: Jackie Manuscript NRN 050713 LPB
Date: Friday, May 24, 2013 12:38:00 PM
Attachments: Jackie Manuscript NRN 050713 LPB.doc

Luc-

A few comments – we have clincaltrials.gov registration numbers for both SUPPORT and GDB – I added them. Also – the rate of late onset sepsis has dramatically declined 40 to 23% - any thoughts??

Thanks
Rose

CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

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Short title: Changes associated with SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: ~~not applicable~~ NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD SUPPORT trial showed that continuous positive airway pressure is an alternative to endotracheal intubation for delivery room therapy in very preterm infants.

What This Study Adds: The proportion of endotracheal intubation significantly decreased after the SUPPORT trial in NICHD centers that participated in the SUPPORT

Revised 5/7/13 3 PM

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 231 words
Article length: 2,059 words

Abstract

Introduction
In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare care process and outcomes before SUPPORT and after its publication.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one. The proportion of DR intubation decreased only in centers with >=80% DR intubation prior to SUPPORT.

Discussion:
This study is limited by its observational before/after design.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ths weeks to $27^{6/7}$ths weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within one hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in May~~June~~ 2010. The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of the current study was to determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal

intubation in the DR in preterm inborn infants. We hypothesized that publication of SUPPORT would be followed by a decrease in proportion of intubation in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We hypothesized that the decrease in proportion of intubation in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. We also aimed to determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks, including risk of death or BPD (defined by oxygen use at 36 weeks of postmenstrual age (PMA)), death or severe ROP (defined as ROP surgery or retinal detachment) at the time of discharge and death before discharge. We also hypothesized that publication of SUPPORT would not affect the risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP (defined as ROP surgery or retinal detachment), and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second birth cohort of patients starting after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those in the SUPPORT trial. Eligible infants were inborn at $24^{0/7}$th to $27^{6/7}$th weeks at birth by best obstetrical estimate, without known malformations, delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study span of the study (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. We included patients who died early, but excluded patients whose support was either withheld or withdrawn.

Baseline variables

Neonatal and maternal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were the intubation in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP

surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Secondary outcome variables:

Secondary outcomes of interest included BPD, severe ROP and other ROP outcomes, deaths within 12 hours or by 36 weeks PMA, surfactant use, DR outcomes, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and Student t-tests or Wilcoxon tests, as appropriate, for continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. These models included pre-specified prenatal covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted

tests, and that preceded the outcome. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes. We created a model specific for BPD, considering the following potential covariates: intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch. Additionally, the Cochran-Mantel-Haenszel test was used to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations $\geq 80\%$ (based on pre-SUPPORT proportion at Parkland, an NRN center which did not participate in the Feasibility Trial)[17] and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

Results

There were a total of 6,601 infants born at $24^{0/7}$ to $27^{6/7}$ weeks gestational age during 2003-2004 (n=2,998) or 2010- 2012 (n=3,603) and included in the GDB (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361

were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants. Of these 1,617 infants were in the pre-SUPPORT group and 2,232 infants were in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, $p<0.001$), maternal hypertension (27.4% vs. 19.9%, $p<0.001$), maternal diabetes (5.4% vs. 2.6%, $p<0.0001$), cesarean section delivery (66.3% vs. 62.1%, $p=0.0078$), and prolonged rupture of membranes (24.1% vs. 27.5%, $p=0.017$) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR intubation and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89),, and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2). Secondary outcomes are shown in Tables 3 and 4. The adjusted risks of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risks of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly

different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the delivery room during the first and second epochs in the 11 centers in the study. The correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.17). Centers were also combined into two groups: two centers with pre-SUPPORT percent DR intubations < 80% and nine centers with pre-SUPPORT percent DR intubations ≥ 80%. The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks gestational age born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR intubation and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR intubation decreased significantly only in centers with a high baseline proportion. There were also significant decreases in risk of severe ROP and death or mechanical ventilation at day of life 7 in the group of infants in the post-SUPPORT group. These findings suggest that the results of SUPPORT trial influenced

both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design which could introduce changes in patient population and secular trends. Since this proposal includes several outcome variables, it is likely that some differences will reach a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on other studies besides the SUPPORT trial.

Conclusion

After adjustment for baseline variables, the risks of DR intubation, ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT results. The adjusted risks of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risks of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after

SUPPORT. These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013

References

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
(Maternal??)Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room epinephrine **	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min.	4.4 (2.5)	3.9 (2.4)	<0.0001
Apgar score, 5 min.	6.5 (2.0)	6.3 (2.2)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	13 (0.8)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge ,and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate
[4] survivors to discharge or 120 days, whichever came first, max is 120 days.
**Lisa needs to take a closer look at this definition before finalized

Figure 1

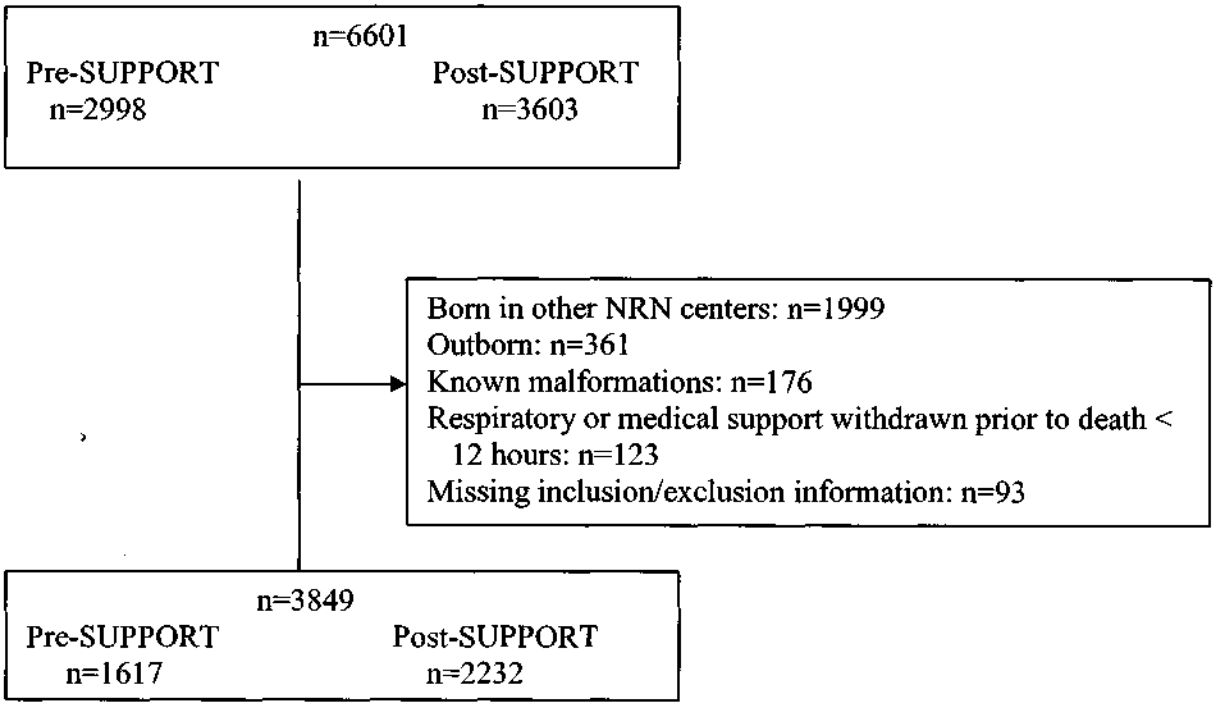
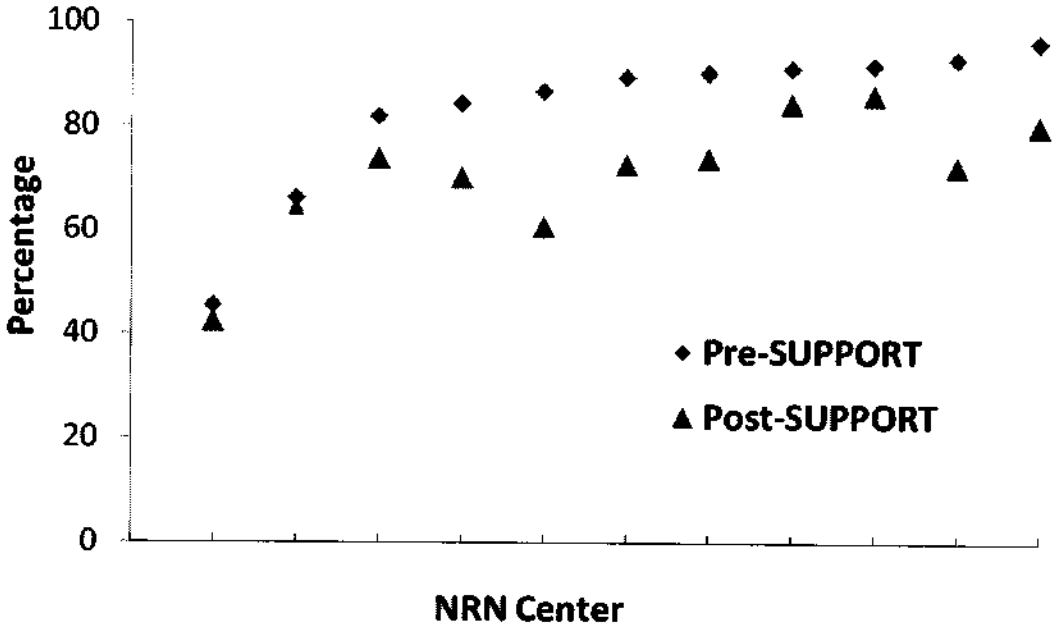


Figure 2



From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: CONFIDENTIAL
Date: Friday, May 24, 2013 10:01:00 AM

WALLY IT IS!!
Do you have time for a brief chat?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, May 24, 2013 10:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CONFIDENTIAL

Hi Rose:

It is best to put my name as Wally. As a true joke, I learned Waldemar was my name when the kindergarten teacher was trying to make me write Waldemar, and my father had to give permission for them to change it officially to Wally ☺.

Wally

Wally Carlo, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 24, 2013 8:48 AM
To: Wally Carlo, M.D.
Subject: RE: CONFIDENTIAL

Wally
I have updated the presentation -- this is very close to final. I will likely move the last two slides either out or into the body of the presentation. Do I have you title correct?

I have discussed with our leadership –
I will present first, you second and Alan Guttmacher third.

Thanks
Rose

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, May 23, 2013 9:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: CONFIDENTIAL

Rose.

Thanks. I will remove the secondary outcomes.

Wally

-----Original message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
Sent: Thu, May 23, 2013 23:00:37 GMT+00:00
Subject: Re: CONFIDENTIAL

Wally
This is excellent- if you feel you need to delete some slides, the secondary outcomes from the main trial could be omitted. There is 1 hour allocated to SUPPORT. Alan will make a few comments. My talk is probably 7-8 minutes. You (+questions or comments from council) get the rest! Sometimes allocated time slots go over...

Thanks for doing this and coming to the meeting

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, May 23, 2013 05:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CONFIDENTIAL

Rose:

See my ppt. It may be too long. I wanted to review the literature and our results. I have to cut it to stay within the allotted 20 min.

I could take out secondary outcomes of SUPPORT. I could also take out saturation results of SUPPORT. What do you think?

Wally

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 22, 2013 9:51 AM
To: Wally Carlo, M.D.
Subject: CONFIDENTIAL

Wally
Here is a draft of my planned presentation for the June 6 council meeting – it has not yet been totally vetted through the clearance process. Slides 14 and 15 are subject to change.

I am happy to discuss by phone if you like. My understanding is that Alan will start, I will present, and then you will present the SUPPORT Trial.

Thanks for coming to this meeting!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rosenthal, Mike (NIH/NICHD) [C]
Subject: RE: PREW, CC-CHOC and CRE KFC discussion about NICU research
Date: Friday, May 24, 2013 9:32:06 AM

I would check with Alan and Yvonne. Ok by me.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 24, 2013 9:31 AM
To: Willinger, Marian (NIH/NICHD) [E]
Cc: Rosenthal, Mike (NIH/NICHD) [C]
Subject: FW: PREW, CC-CHOC and CRE KFC discussion about NICU research

Marian
I was asked to be on this call to discuss the SUPPORT Trial – is this acceptable? I serve on the CC-CHOC Drug committee – this is the Ethics committee

Thanks
Rose

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From: CTSA Child Health [mailto:CTSA_ChildHealth@CTSAC4.Org]
Sent: Wednesday, May 22, 2013 2:33 PM
To: CC-CHOC Listserv (list.cc-choc@ctsacentral.org); PREW Listserv (list.cc-choc.prew@ctsacentral.org)
Subject: PREW, CC-CHOC and CRE KFC discussion about NICU research

Dear CC-CHOC and PREW members,

Please see the email below from Ben Wilfond about an upcoming discussion on the SUPPORT study. The meeting will take place on July 2nd, 2013 from 11:30am to 1:00pm ET. Click here to register.

I am writing in my role as the chair of the Clinical Research Ethics KFC Consultation Working Group, we discussed the SUPPORT study on our recent steering committee call this week. I am assuming you are aware of this but if not, this the study in the NICU comparing different standard approaches to oxygen delivery that has resulted in an OHRP investigation based on advocacy from Public Citizen.

This has become sensationalized in the media, and may have implications for further NICU research designed to improve quality of care, using rigorous methodological approaches. I am particularly interested in this issue as I am pediatric pulmonologist who regularly cares for such children in the NICU.

Our Working Group will be having a quarterly call on July 2 where we will be discussing this case to understand it better. I thought that members of the PREW and CC-CHOC might interesting in joining. Further I was interested in knowing this was being discussed by these other groups, or other places within the CTSA leadership. Our group is also considering writing a paper about the implications of this study either for us as consultants for CTSAs. (we do not have a clear ides of this implications yet).

I am ccing others whom I thought might interested in knowing of the interest of our Working Group

ben

Benjamin Wilfond MD
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--

From: Luc Brion
To: Wrage, Lisa Ann; Gantz, Marie; Pablo Sanchez; Myra Wyckoff; Roy Heyne; Mambarambath Jaleel; M.D." <WCarlo@peds.uab.edu>, ""; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Jackie LeVan; Archer, Stephanie (NIH/NICHD) [E]
Subject: Jackie LeVan Manuscript on Changes after SUPPORT
Date: Thursday, May 23, 2013 10:38:22 PM
Attachments: Jackie Manuscript NRN 050713 LPB.doc

Here is the manuscript I sent you on April 7 for comments.
Please let me know if this manuscript is ready to be submitted.

Rose and Stephanie:
Please let me know what boiler plate should be used, or if there is any process I should follow
Thanks
Luc

Luc P. Brion, MD
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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO,[1,2] Luc P Brion, MD,[1] Lisa Wrage, MPH,[3] Marie Gantz, PhD,[3] Myra H Wyckoff, MD,[1] Pablo Sánchez, MD,[1] Roy Heyne, MD,[1] Mambarambath Jaleel,[1] MD, Neil Finer, MD,[4] Waldemar Carlo, MD,[5] Abhik Das, PhD,[3] Barbara Stoll, MD,[6] Rose Higgins, MD,[7] on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: [1]University of Texas Southwestern, Dallas, TX; [2] Current affiliation: Pediatrix Medical Group, San Antonio, TX; [3]RTI International, Research Triangle Park, NC; [4]University of California, San Diego, CA; [5]University of Alabama, Birmingham, AL; [6]Emory University, Atlanta, GA; [7]Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Changes associated with SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

Clinical Trial registration: not applicable

What's known on This Subject: The NICHD SUPPORT trial showed that continuous positive airway pressure is an alternative to endotracheal intubation for delivery room therapy in very preterm infants.

What This Study Adds: The proportion of endotracheal intubation significantly decreased after the SUPPORT trial in NICHD centers that participated in the SUPPORT

Revised 5/7/13 3 PM

Contributors' Statement Page

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.
Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.
Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.
Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Waldemar Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Barbara Stoll: Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.
Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 231 words
Article length: 2,059 words

Abstract

Introduction
In the NICHD Neonatal Research Network (NRN) SUPPORT trial preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of this study was to compare care process and outcomes before SUPPORT and after its publication.

Methods:
This was a retrospective cohort study using the prospective NRN generic database. We included infants $24^{0/7}$-$27^{6/7}$ weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received comfort care. The primary outcomes were DR intubation, bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

Results:
After adjustment for baseline variables, the RRs for DR intubation, ROP/death, BPD/death and death at discharge were significantly lower than one. The proportion of DR intubation decreased only in centers with >=80% DR intubation prior to SUPPORT.

Discussion:
This study is limited by its observational before/after design.

Conclusions:
After adjustment for baseline variables infants $24^{0/7}$-$27^{6/7}$ weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

Introduction:

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of $24^{0/7}$ths weeks to $27^{6/7}$ths weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within one hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.[1,2] The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in June 2010. The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA $24^{0/7}$ weeks to $25^{6/7}$ weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of the current study was to determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal

intubation in the DR in preterm inborn infants. We hypothesized that publication of SUPPORT would be followed by a decrease in proportion of intubation in the DR in preterm infants $24^{0/7}$ to $27^{6/7}$ weeks. We hypothesized that the decrease in proportion of intubation in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. We also aimed to determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between $24^{0/7}$ and $27^{6/7}$ weeks, including risk of death or BPD (defined by oxygen use at 36 weeks of postmenstrual age (PMA)), death or severe ROP (defined as ROP surgery or retinal detachment) at the time of discharge and death before discharge. We also hypothesized that publication of SUPPORT would not affect the risk of death or BPD at 36 weeks PMA, death before discharge or severe ROP (defined as ROP surgery or retinal detachment), and death before discharge.

Methods

Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second birth cohort of patients starting after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those in the SUPPORT trial. Eligible infants were inborn at $24^{0/7}$th to $27^{6/7}$th weeks at birth by best obstetrical estimate, without known malformations, delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study span of the study (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1^{st} cohort) or medical therapy (2^{nd} cohort) withheld or withdrawn at any time prior to death < 12 hours. We included patients who died early, but excluded patients whose support was either withheld or withdrawn.

Baseline variables

Neonatal and maternal characteristics of interest include birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variables:

The primary outcome variables were the intubation in DR, the composite of death or BPD (oxygen use at 36 weeks of PMA), the composite of severe ROP (defined as ROP

surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Secondary outcome variables:

Secondary outcomes of interest included BPD, severe ROP and other ROP outcomes, deaths within 12 hours or by 36 weeks PMA, surfactant use, DR outcomes, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use, patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)[5] and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables and Student t-tests or Wilcoxon tests, as appropriate, for continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. These models included pre-specified prenatal covariates (based on the literature) as well as additional covariates that were significantly different by study group in the unadjusted

tests, and that preceded the outcome. Multivariate models included NRN center and prenatal covariates shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment).[6] Additional perinatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis were also used as covariates: race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes. We created a model specific for BPD, considering the following potential covariates: intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.[7-16]

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first epoch (pre-SUPPORT) to the second epoch (post-SUPPORT) was higher in centers with higher proportion of intubation during the first epoch. Additionally, the Cochran-Mantel-Haenszel test was used to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations $\geq$ 80% (based on pre-SUPPORT proportion at Parkland, an NRN center which did not participate in the Feasibility Trial)[17] and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

Results

There were a total of 6,601 infants born at $24^{0/7}$ to $27^{6/7}$ weeks gestational age during 2003-2004 (n=2,998) or 2010- 2012 (n=3,603) and included in the GDB (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361

were outborn, these infants were excluded. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants who had missing inclusion/exclusion information were excluded, leaving a total study population of 3,849 infants. Of these 1,617 infants were in the pre-SUPPORT group and 2,232 infants were in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%, p<0.001), maternal hypertension (27.4% vs. 19.9%, p<0.001), maternal diabetes (5.4% vs. 2.6%, p<0.0001), cesarean section delivery (66.3% vs. 62.1%, p=0.0078), and prolonged rupture of membranes (24.1% vs. 27.5%, p=0.017) in the Post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcomes, unadjusted comparisons showed a significant decrease in the proportion of DR intubation and the risk of death or BPD, death or ROP, and death in the post-SUPPORT group. The adjusted risk of DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89),, and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT (Table 2). Secondary outcomes are shown in Tables 3 and 4. The adjusted risks of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group. In contrast, the risks of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly

different between groups. Average ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT (Table 3). Unadjusted comparisons are shown in table 4.

Figure 2 shows the proportion of infants intubated in the delivery room during the first and second epochs in the 11 centers in the study. The correlation between the proportion of intubations in the delivery room during the first epoch and the change in proportion of intubations in the delivery room from the first to the second epoch was not significant (Spearman correlation coefficient -0.44, p=0.17). Centers were also combined into two groups: two centers with pre-SUPPORT percent DR intubations < 80% and nine centers with pre-SUPPORT percent DR intubations ≥ 80%. The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Discussion:

Infants $24^{0/7}$ to $26^{6/7}$ weeks gestational age born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR intubation and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. The proportion of DR intubation decreased significantly only in centers with a high baseline proportion. There were also significant decreases in risk of severe ROP and death or mechanical ventilation at day of life 7 in the group of infants in the post-SUPPORT group. These findings suggest that the results of SUPPORT trial influenced

both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two epochs. Limitations of this study include the observational design, which introduce confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design which could introduce changes in patient population and secular trends. Since this proposal includes several outcome variables, it is likely that some differences will reach a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. It is possible that additional unknown biases or confounding variables could have affected the results. Some centers may have changed practice guidelines and providers may have changed their practice based on other studies besides the SUPPORT trial.

Conclusion

After adjustment for baseline variables, the risks of DR intubation, ROP/death, BPD/death, and death before discharge for preterm neonates $24^{0/7}$-$27^{6/7}$ weeks' GA born at Network Centers decreased following the publication of SUPPORT results. The adjusted risks of severe ROP and of death or mechanical ventilation at day of life seven also decreased significantly. In contrast, the risks of death at 36 weeks PMA and of BPD did not change significantly. Average ventilator days among survivors decreased after

SUPPORT. These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Acknowledgments:

We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California – San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013

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Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT epoch for the eleven Neonatal Research Network Centers included in this study

Table 1. Maternal and Neonatal Characteristics[1]

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

[1] presented as mean (SD) for continuous variables, and n (%) for categorical variables.
[2]The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcomes

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Adjusted RR[3] (95% CI)	Adjusted p-value[3]
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	0.86 (0.76-0.98)	0.02

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk
[1] presented as n (%)
[2] unadjusted p-values from Chi-Square tests
[3] adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

Table 3. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]	Difference in Means[3] (95% CI)	adjusted RR[3] (95% CI)	Adjusted p value
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	
Days on ventilator (survivors)[4]	22.3 (24.4), 13	17.8 (21.3),9.0	<0.0001	-4.7 (-6.1, -3.2)		<.0001

[1] presented as mean (SD), median for days on ventilator and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate
[3] adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table4. Secondary Outcomes[1]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value[2]
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room epinephrine **	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min.	4.4 (2.5)	3.9 (2.4)	<0.0001
Apgar score, 5 min.	6.5 (2.0)	6.3 (2.2)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	13 (0.8)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors)[4]	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors)[4]	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

[1] presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge ,and length of hospital stay; mean (SD) for all other continuous variables, and n (%) for categorical variables.
[2] unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate
[4]survivors to discharge or 120 days, whichever came first, max is 120 days.
**Lisa needs to take a closer look at this definition before finalized

Figure 1

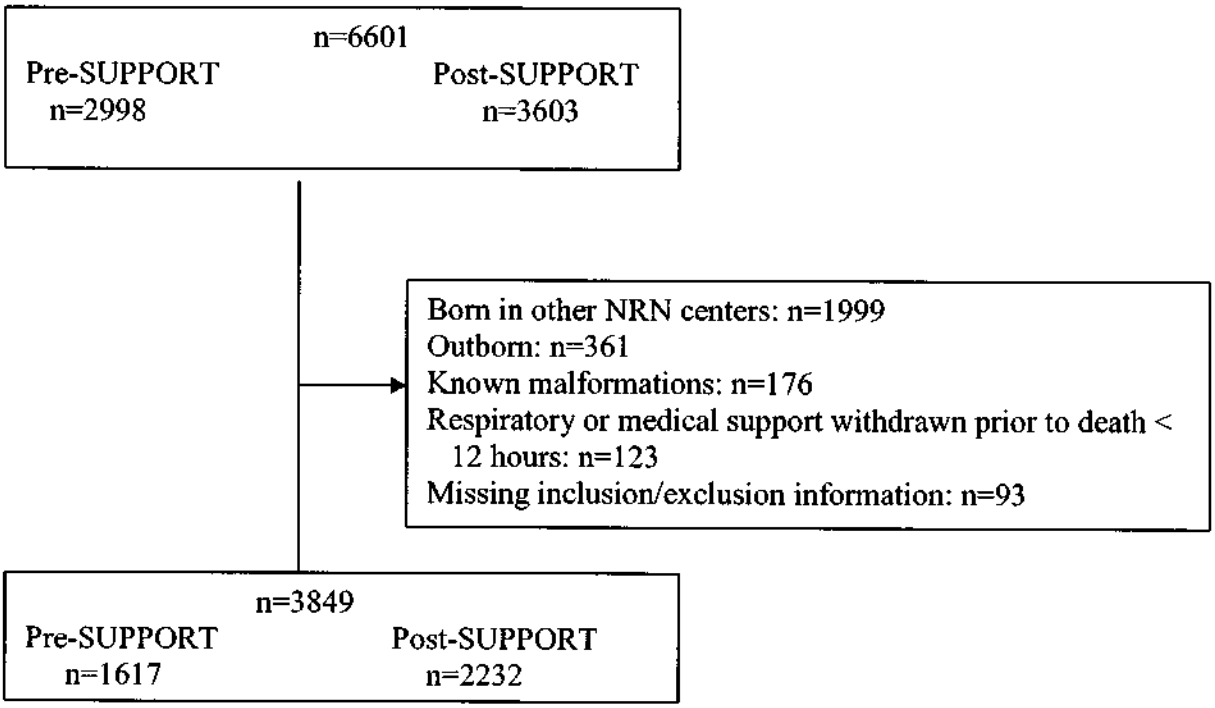
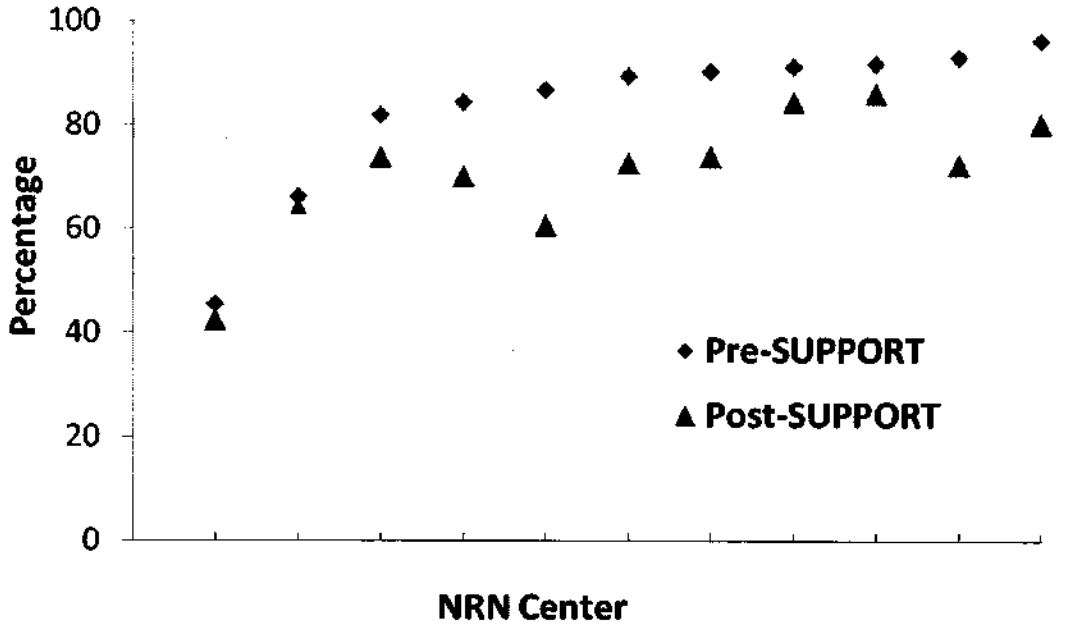


Figure 2



From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CONFIDENTIAL
Date: Thursday, May 23, 2013 5:17:48 PM
Attachments: SUPPORT Wally Carlo.ppt

Rose:

See my ppt. It may be too long. I wanted to review the literature and our results. I have to cut it to stay within the allotted 20 min.

I could take out secondary outcomes of SUPPORT. I could also take out saturation results of SUPPORT. What do you think?

Wally

Wally Carlo, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 22, 2013 9:51 AM
To: Wally Carlo, M.D.
Subject: CONFIDENTIAL

Wally
Here is a draft of my planned presentation for the June 6 council meeting – it has not yet been totally vetted through the clearance process. Slides 14 and 15 are subject to change.

I am happy to discuss by phone if you like. My understanding is that Alan will start, I will present, and then you will present the SUPPORT Trial.

Thanks for coming to this meeting!!!
Rose

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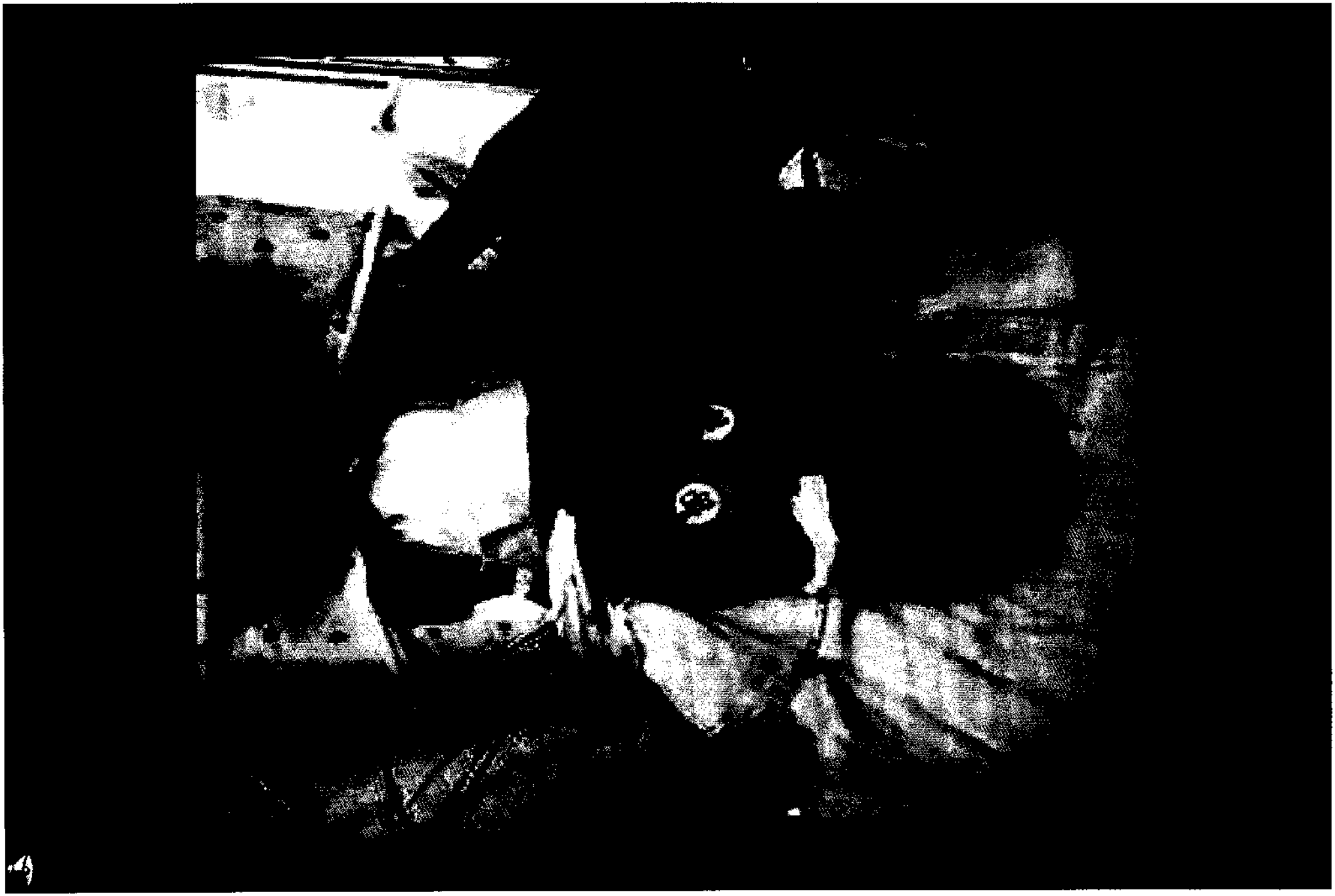
The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Preterm Infants (SUPPORT Trial)

The SUPPORT Study Group of the Eunice Kennedy Shriver
NICHD Neonatal Research Network

4-05241



Stevie Wonder

Famous former preemie; blind from retinopathy

History of Supplemental Oxygen in Preterm Babies

- 1940s - Excessive O_2 use in preemies; retinopathy in premature infants was first observed
- 1950s - Uncontrolled O_2 (<50% FiO_2, severe hypoxia allowed) restriction trials led to reduced retinopathy (not blindness) but trends for increased mortality (4% increase)
- 1960s - Uncontrolled O_2 was estimated to result in 16 deaths per case of blindness prevented
- 2010 - SUPPORT trial: O_2 titration to keep saturations 85-89% in preemies resulted in decreased retinopathy (not blindness) but increased death (3.7%)
- 2013 - BOOST II and COT trials confirm SUPPORT trial results

Objectives

1. Know the results of the SUPPORT RCT arm of lower versus high oxygen saturation targeting
2. Understand the limitations of using the results for changes in clinical practice
3. Be able to apply the results of this trial in your daily practice

Background

- No consensus on oxygen saturation targets
- Published "acceptable" levels in neonates were initially 88-98% and more recently 85-95%
- No standards for assessing "need" for oxygen supplementation in infants

Does oxygen saturation targeting matter?

Previous Trials of Oxygenation Targets

STOP-ROP Trial

BOOST I Trial

SaO_2 Targets: STOP-ROP Trial

Methods

Design:	Multicenter RCT, not masked
Patient population:	649 preterm infants with prethreshold ROP
Treatment group:	O_2 sat 96-99% or 89-94%
Primary outcome:	Progression to threshold ROP in at least one eye

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

SaO_2 Targets: STOP-ROP Trial

	Sats 96 to 99%	Sats 89 to 94%	p value
Threshold ROP	41%	48%	<0.05
Pneumonia/BPD exacerbations	13%	8%	= 0.07
Prolonged hospitalization*	13%	7%	<0.05
Prolonged oxygen*	47%	37%	<0.05
Prolonged diuretics*	36%	24%	<0.05
Death	3%	2%	NS

* At 3 months corrected age

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

SaO_2 Targets: BOOST Trial

Methods

Design:	Multicenter RCT, double blind
Patient population:	358 infants born at < 30 weeks and oxygen dependent at 32 weeks
Treatment groups:	SaO_2 95-98% or 91-94%
Primary outcome:	Growth and neurodevelopment at 12 months corrected age

Askie et al. NEJM 349:959, 2003

SaO_2 Targets: BOOST Trial

	Sats 95-98%	Sats 91-94%	p value
Dev abnormality	23%	24%	NS
Weight < 10% tile	33%	37%	NS
Death	5%	3%	NS
O_2 at 36 w	64%	46%	<0.001
Home O_2	30%	17%	<0.001

Askie et al. NEJM 349:959, 2003

Previous Trials of Oxygen Saturation Targets

STOP-ROP Trial
BOOST I Trial

1. Both targeted oxygen saturation at upper limits of practice (high 90s)
2. Both were post-neonatal interventions
3. Both reported pulmonary harms

How about studies of oxygen saturation targets below 90%?

Before SUPPORT, there had not been randomized controlled trials of oxygen saturation targets below 90%

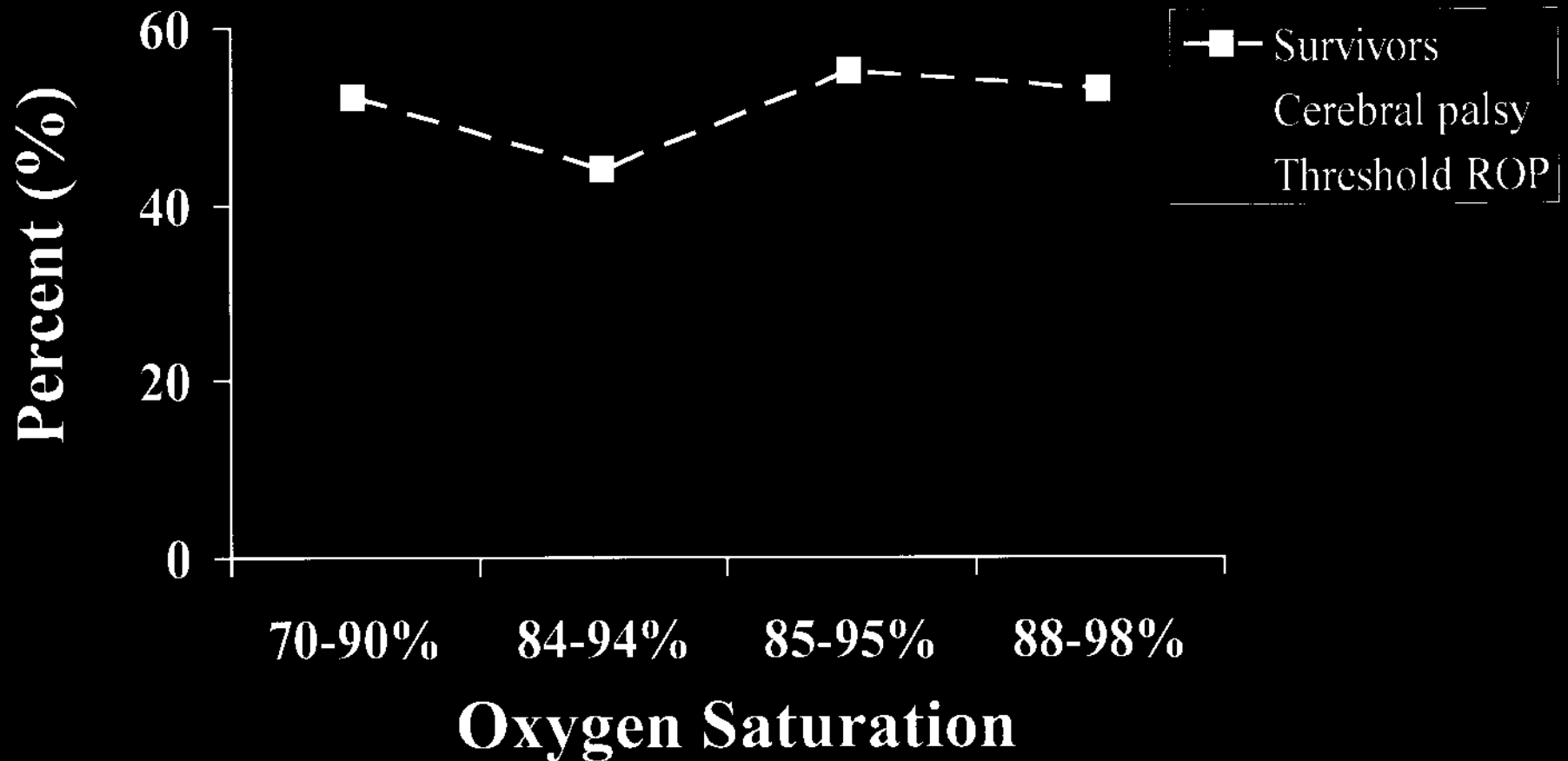
SaO_2 Targets: Retrospective Study

Methods

- Retrospective review
- Population study - All babies < 28 weeks in several referral units
- Data analyzed by SaO_2 targets

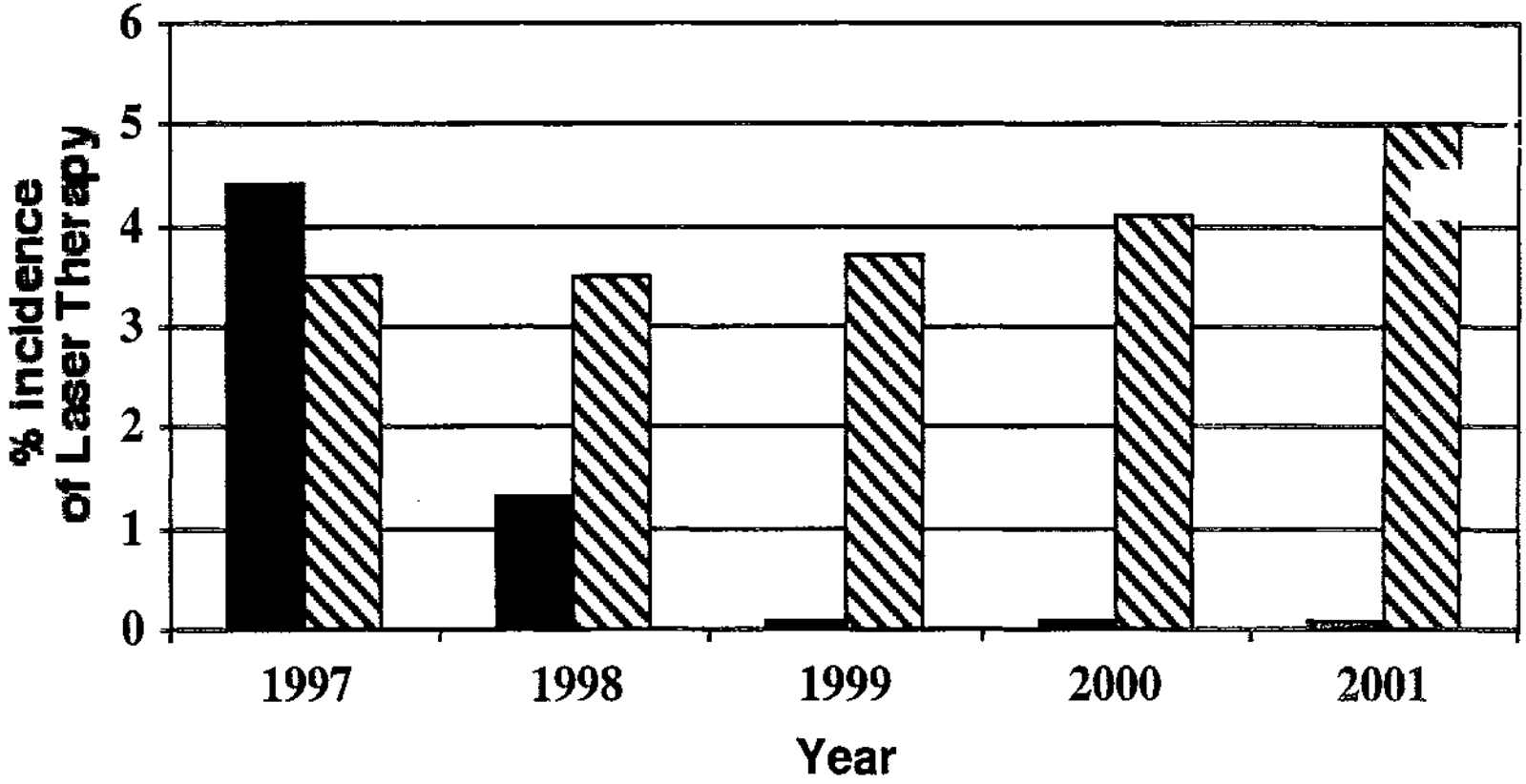
Tin et al. Arch Dis Child. 84:F106, 2001

SaO_2 Targets: Retrospective Study



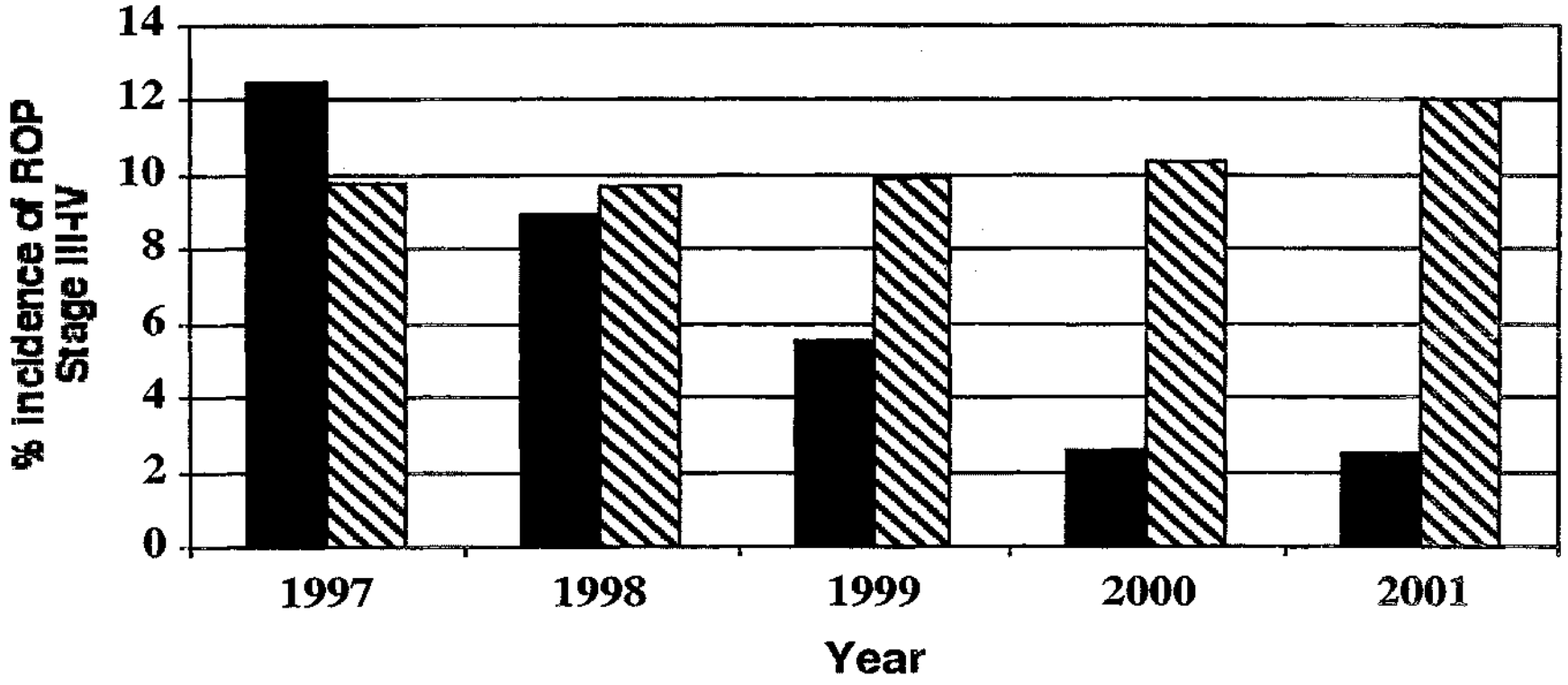
Tin et al. Arch Dis Child. 84:F106, 2001

Incidence of ROP Laser Therapy for Infants with Birth Weight of 500-1500 g



Chow LC et al. Pediatrics 111:339, 2003

Incidence of ROP Stages 3 to 4 for Infants with Birth Weight of 500-1500 g



Chow LC et al. Pediatrics 111:339, 2003

What oxygen saturation targets were physicians using?

SaO_2 Targets: Expert Opinion

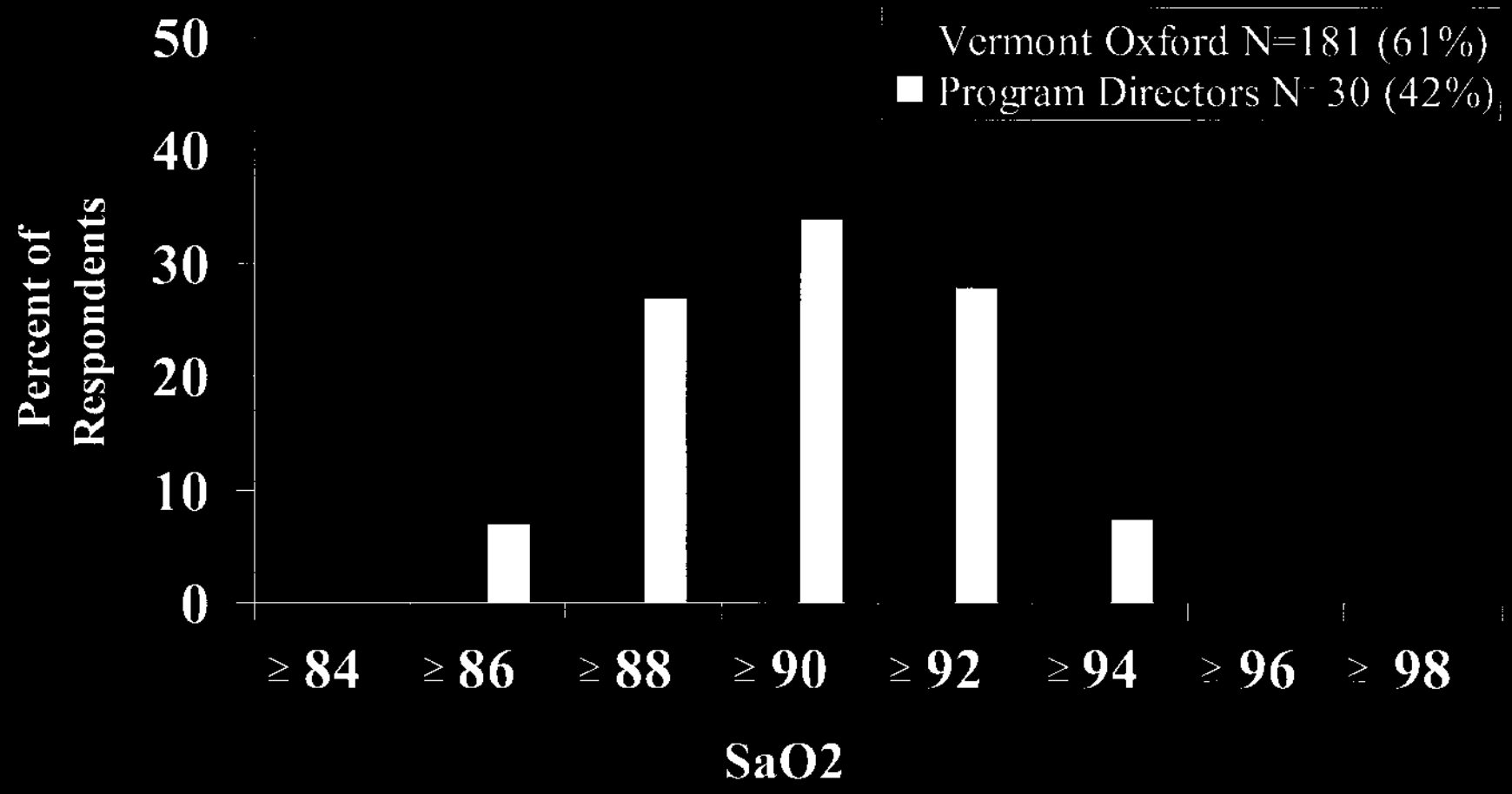
Methods

Design: Survey of VON Centers and ONTPD

Respondents: 181 (61%) VON Centers and 30 (42%) PD

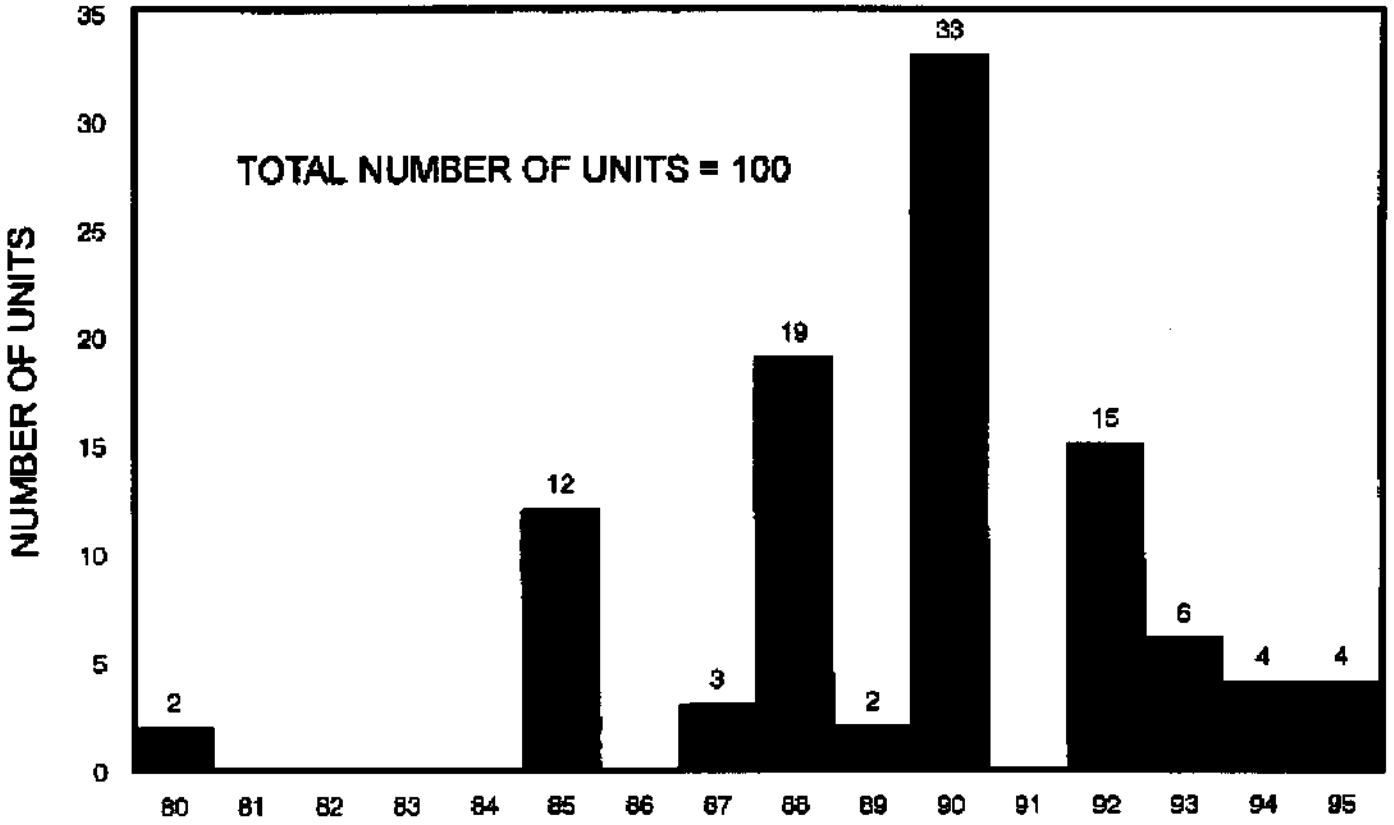
Ellsbury et al. J Pediatr 140:247, 2002

SaO_2 Targets: Expert Opinion



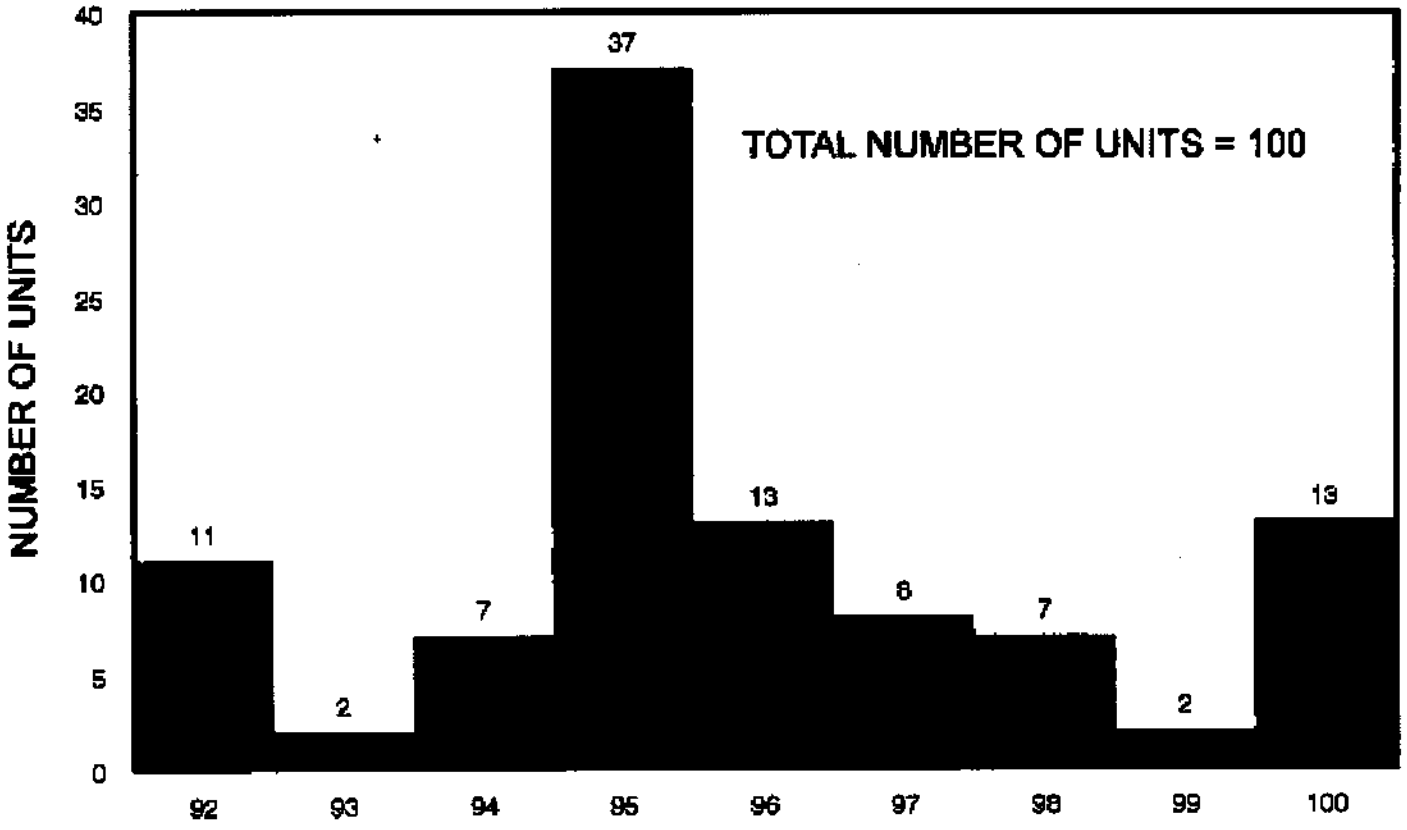
Ellsbury et al. J Pediatr 140:247, 2002

Minimum Acceptance Arterial Pulse Oxygen Saturation



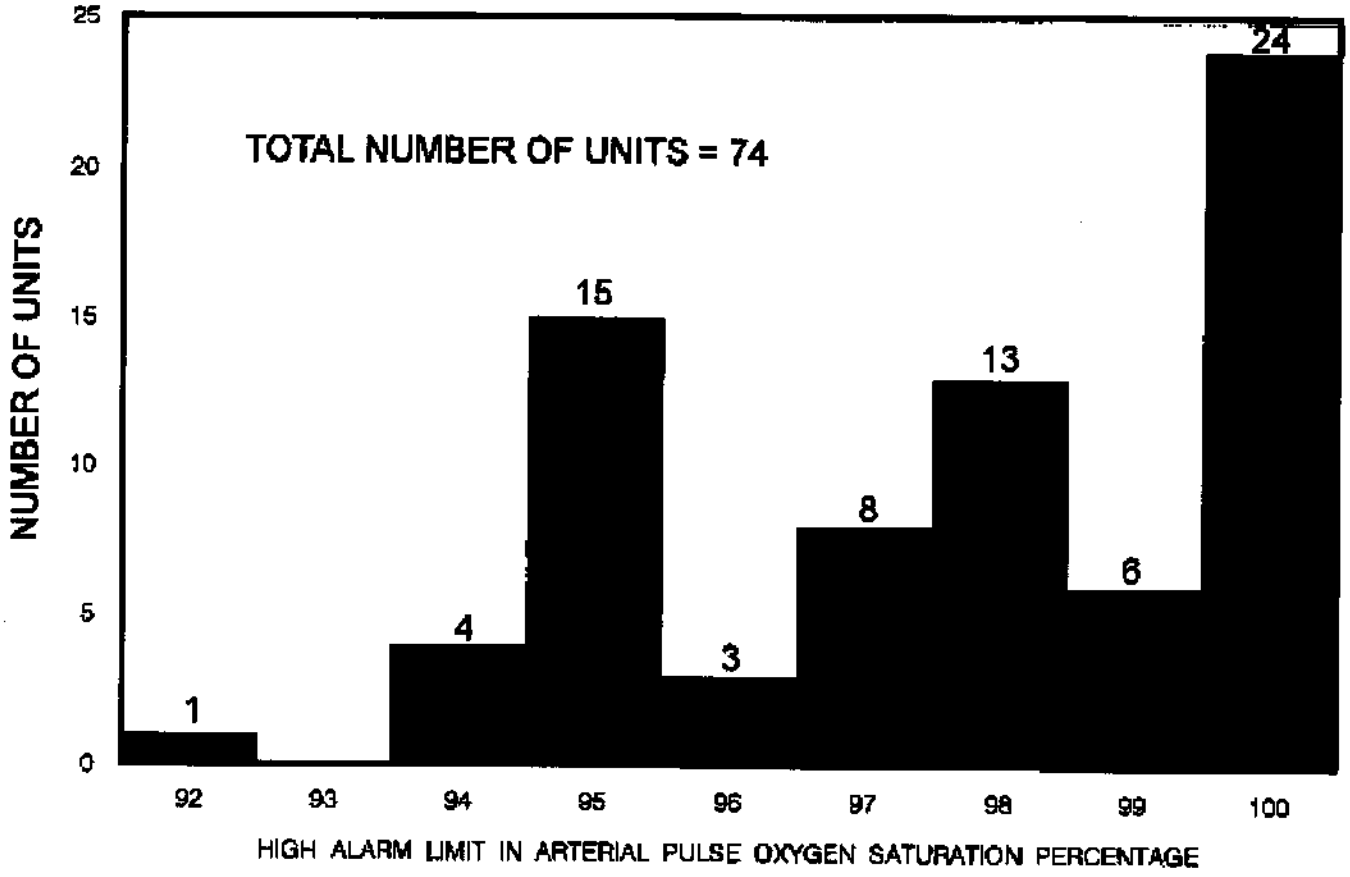
Vijayakumar et al. J Perinatol 17:341, 1997

Maximum Acceptance Arterial Pulse Oxygen Saturation



Vijayakumar et al. J Perinatol 17:341, 1997

Value at Which High Arterial Pulse Oxygen Saturation Alarm is Set



Vijayakumar et al. J Perinatol 17:341, 1997

What actual oxygen saturations were achieved before the SUPPORT Trial?

Current O_2 Targets and Practice

Design: Prospective multicenter observational study

Patient Population:
- 84 infants <28 week, <96 hours in 14 centers in 3 countries, monitored for 4 weeks
- Birthweight 863 $\pm$ 208 grams
- Gestational age 26 $\pm$ 1 week

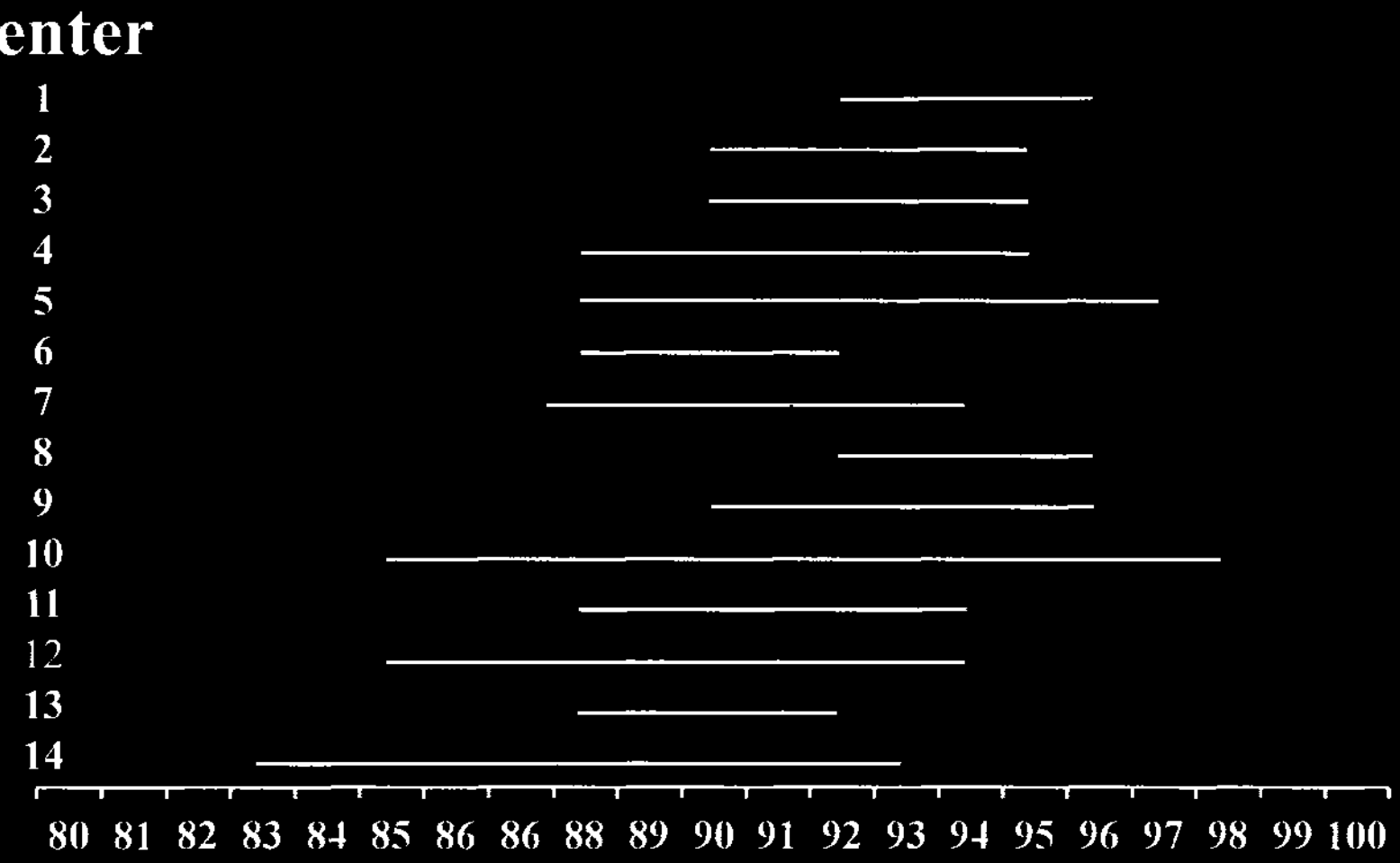
Hagadorn et al. Pediatrics 118:1574, 2006

Targets Used at Centers

		# of Centers
Included only targets 91-95%	–	7
Included only targets 85-89%	–	2
Included both targets	–	1
Included neither target	–	4

Hagadorn et al. Pediatrics 118:1574, 2006

Oxygen Saturation Used by Center



Hagadorn et al. Pediatrics 118:1574, 2006

Median Saturation Achieved in Centers

Overall Median Oxygen Saturation was 95%

Compliance With Targets
Percentage of Monitored Time

	Percent, (25^{th}-75^{th})
Below intended range	16%, (0-47%)
Within intended range	48%, (6-75%)
Above intended range	36%, (5-90%)

Background - SUPPORT Oxygen Saturation Trial

- Retinopathy of prematurity (ROP) continues to be an important cause of blindness in preterm infants
- Recent observational data suggest that oxygen saturations in the lower limits of common clinical practice (83 or 85%) may reduce ROP but this has not been tested in RCTs
- Furthermore, in RCTs of oxygen supplementation to reduce ROP conducted in the 1950s, restriction of oxygen supplementation without oxygenation measurements resulted in an increased mortality in infants in the lower oxygen group

Hypothesis

Among infants of 24 $^{0/7}$ to 27 $^{6/7}$ weeks gestational age

a lower O_2 saturation target range (85 to 89%)

compared to

a higher O_2 saturation target range (91 to 95%) reduces

the incidence of the composite outcome of severe

ROP or death

Method – Patients

- Inborn infants of 24 $^{0/7}$ to 27$^{6/7}$ weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained antenatally
- Enrollment was conducted from February 2005 to February 2009
- Randomization was stratified by center and by gestational age:
  - 24 and 25 weeks
  - 26 and 27 weeks

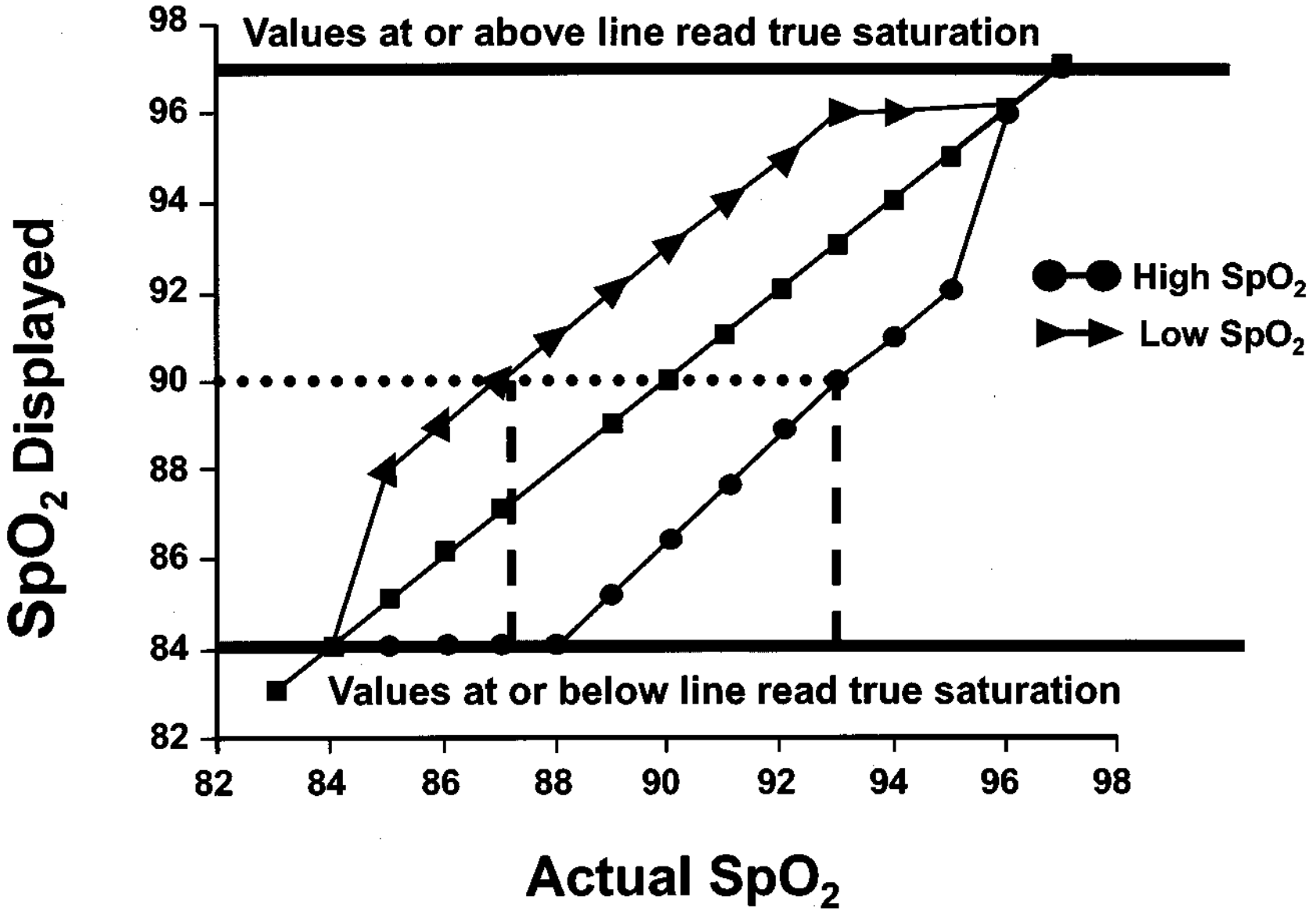
Methods – Intervention (1)

- Infants were randomized to:
  - lower saturation targeting (85 to 89%) or;
  - higher saturation targeting (91 to 95%)

- Oxygen saturations were monitored with electronically-altered Masimo Radical Pulse Oximeters

SpO_2 Group	Displayed	Actual Target	Alarm Values
Low SpO_2	88-92%	85-89%	<85 and >95%
High SpO_2	88-92%	91-95%	<85 and >95%

Actual vs Low and High Reading SpO_2



Recent Trials of Oxygenation Targets

	Experimental	Control
SUPPORT, BOOST II, COT	85-89%	91-95%
STOP-ROP	96-99%	89-94%
BOOST I	95-98%	91-94%

Methods – Intervention (2)

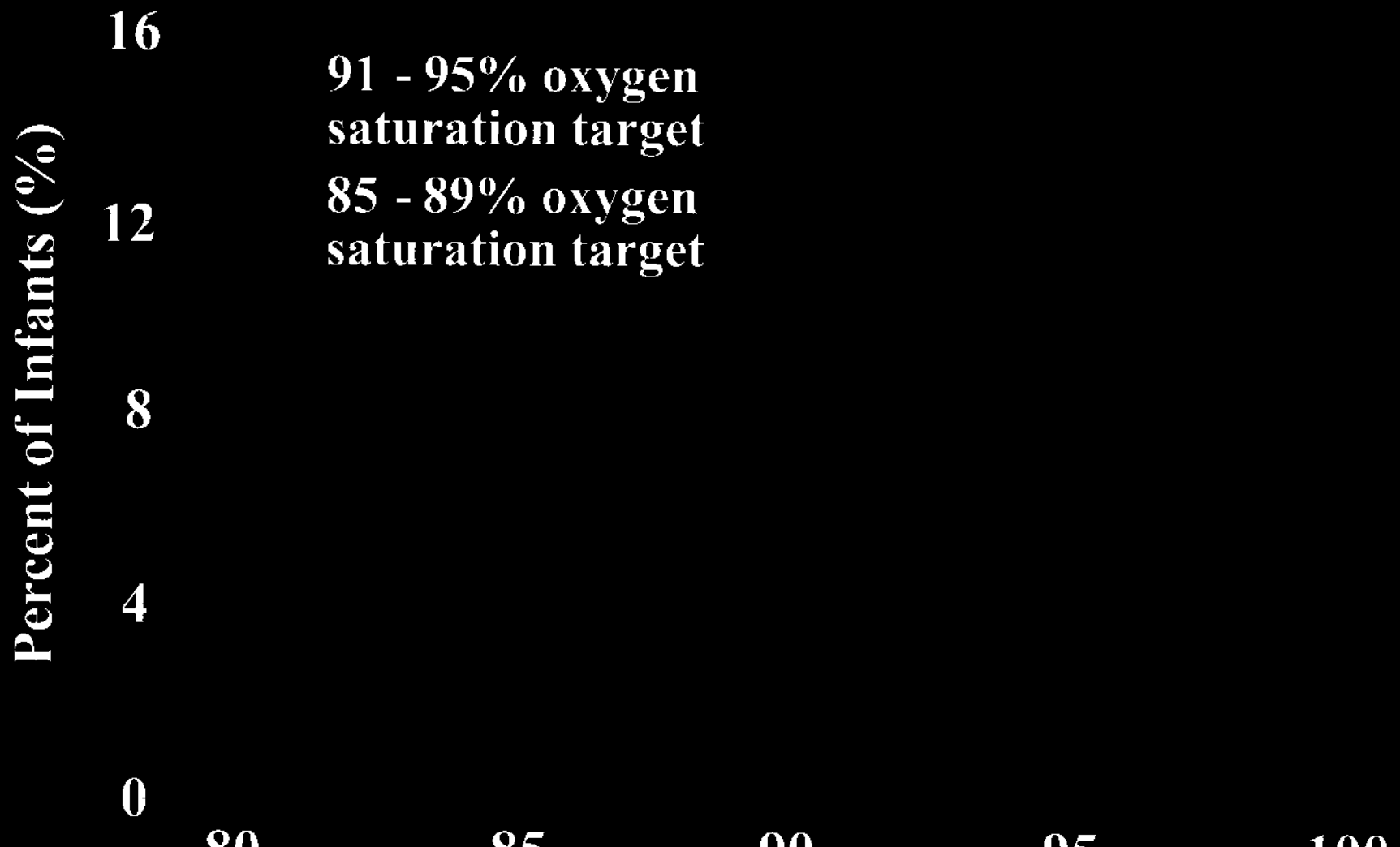
- Oxygen saturation targeting from birth (< 2 hrs) to 36 weeks post-menstrual age or on room air and off the ventilator/CPAP for >72 hours, whichever occurred first
- Adjustments in supplemental oxygen to maintain the displayed saturation within the target range of 88 to 92% were performed by the clinical staff, not the researchers

Results – Patient Population*

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birth weight	836±193 grams	825±193 grams
Gestational age	26±1 weeks	26±1 weeks
Race, White/Black/Hispanic	37/39/20%	42/35/19%
Antenatal corticosteroids	96.8%	95.6%
Multiple births	24.6%	26.6%

*All p values >0.05

Actual Median Oxygen Saturation (%)

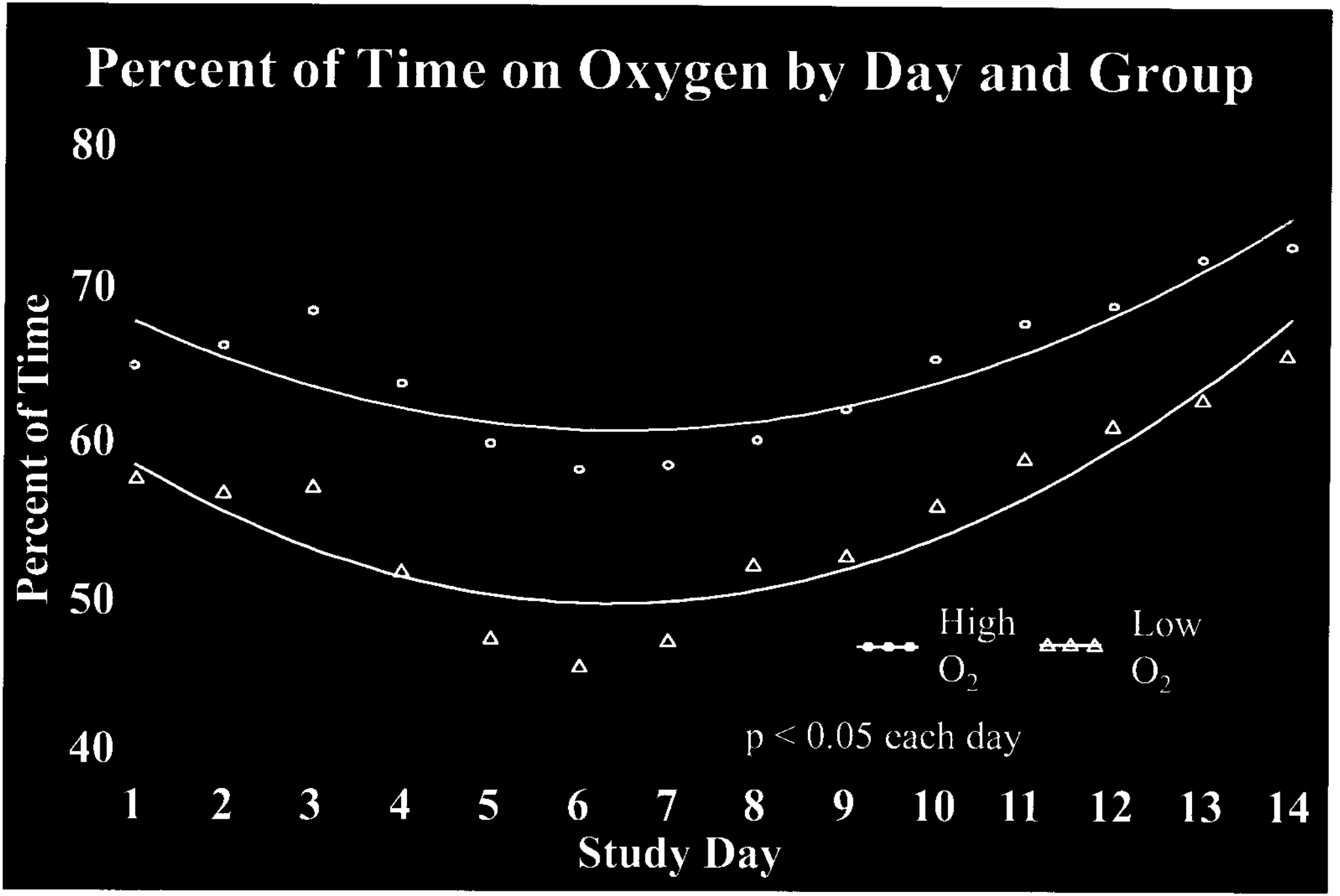


Mean Percent of Time Spent in SpO_2 Ranges While on Supplemental Oxygen

SpO_2 range	Lower Saturation Group Mean % of time in range (95% CI)	Higher Saturation Group Mean % of time in range (95% CI)	p value
>96%	20.1 (18.8, 21.3)	23.2 (22.0, 24.5)	0.001
<85%	7.3 (6.6, 8.1)	5.5 (4.8, 6.3)	0.001
<75%	4.5 (3.8, 5.2)	3.6 (2.9, 4.3)	0.049
<70%	2.5 (1.9, 3.1)	2.1 (1.5, 2.7)	0.409

Median Percent of Time Spent in SpO_2 Ranges While on Supplemental Oxygen

SpO_2 range	Lower Saturation Group Median % of time in range	Higher Saturation Group Median % of time in range	p value
>96%	16.0	19.6	<0.001
<85%	5.9	3.9	<0.001
<75%	3.3	2.1	<0.001
<70%	1.5	0.9	<0.001

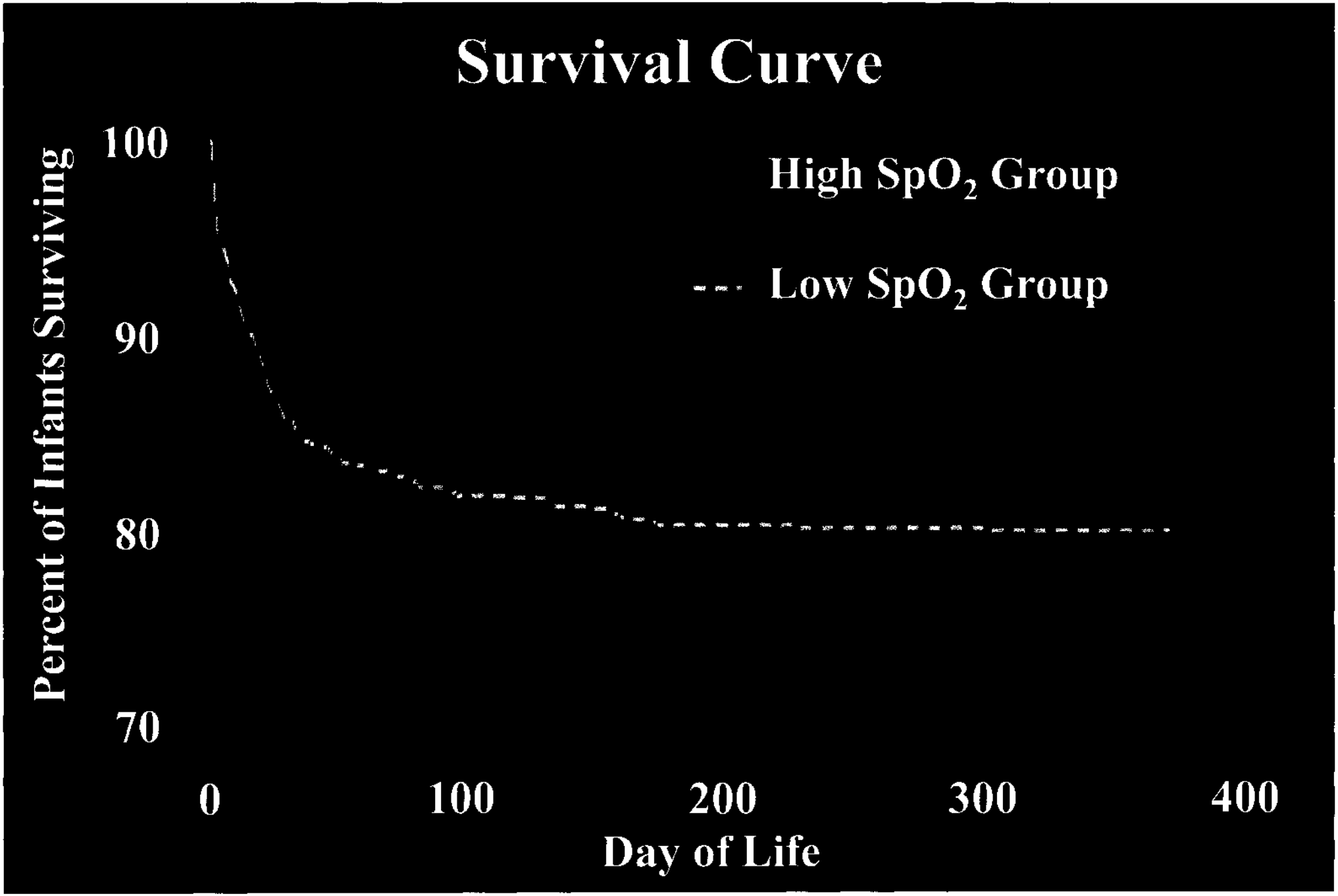


Results – Primary Outcome

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)	
Severe ROP/death	28.3%	32.1%	0.90 (0.76, 1.06)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Death	19.9%	16.2%	1.27 (1.01, 1.60)	NNH=27

Results – ROP Adjudication Analysis

	Lower Saturation Group N=654	Higher Saturation Group N=662	Relative Risk for Low SpO_2 vs. High SpO_2 (95% CI)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Severe ROP with adjudication (98.6%)	8.0%	16.6%	0.52 (0.37, 0.73)	NNT=12
Severe ROP with ROP if lost to F/U (100%)	10.1%	17.5%	0.62 (0.45, 0.84)	NNT=14



Results – BPD and Other Pulmonary Outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
BPD (O_2 use at 36 w)	37.6%	46.7%	0.82 (0.72, 0.93)
BPD (O_2 use) or death, 36 w	48.5%	54.2%	0.91 (0.83, 1.01)
BPD (phys), 36 w	38.0%	41.7%	0.92 (0.81, 1.05)
BPD (phys) or death, 36 w	48.8%	50.0%	0.99 (0.90, 1.10)
Pneumothorax	7.2%	6.5%	1.12 (0.74, 1.68)
Any air leaks (14 days)	7.8%	6.3%	1.23 (0.83, 1.83)
Postnatal steroids for BPD	9.6%	10.7%	0.91 (0.67, 1.24)

Results – PDA

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
PDA	47.9%	50.0%	0.96 (0.86, 1.07)
Medical R_x for PDA	34.5%	36.1%	0.95 (0.82, 1.09)
Surgical R_x for PDA	11.4%	10.5%	1.09 (0.80, 1.48)

Results – Other Major Outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
IVH, grade 3 or 4	13.2%	12.7%	1.06 (0.80, 1.40)
PVL	3.8%	4.7%	0.83 (0.49, 1.42)
NEC, stage ≥ 2	11.9%	10.8%	1.11 (0.82, 1.51)
Late onset sepsis	36.5%	35.6%	1.03 (0.89, 1.18)

Characteristics of the Follow-up Cohorts

Characteristic	Lower Oxygen Saturation N=479	Higher Oxygen Saturation N=511
Birth weight	858±186g	844±192g
Gestational age	26±1w	26±1w
Multiple birth	26%	25%
Antenatal steroids	96%	95%

Vaucher et al. N Engl J Med, 2013

Neurodevelopmental Impairment at 18 to 22 Months

Viable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
Primary outcome determined	94%	94%	1.00 (0.97-1.03)	0.79
Death or NDI	30%	28%	1.12 (0.94-1.32)	0.21
Death	22%	18%	1.25 (1.00-1.55)	0.046
NDI	10%	11%	0.87 (0.60-1.28)	0.49
Bilateral blindness	1%	1%	0.90 (0.28-2.90)	0.86

Vaucher et al. N Engl J Med, 2013

Visual Outcome at 18 to 22 Months

Viable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
Strabismus	9.6%	8.0%	0.80-1.80	0.38
Nystagmus	4.6%	2.5%	0.89-3.69	0.10
Eyes track 180 degrees	97.1%	97.2%	0.98-1.02	0.93
Corrective lenses for both eyes	4.5%	4.1%	0.63-2.10	0.65
Blind with some function in both eyes	0.7%	0.4%	0.27-8.96	0.61
Blind with no useful vision in both eyes	0.4%	0.8%	0.10-2.96	0.48
Other abnormal eye finding	1.3%	2.5%	0.21-1.46	0.23
Blind in at least one eye	1.0%	1.6%	0.22-2.02	0.48

Vaucher et al. N Engl J Med, 2013

Summary

- O_2 saturation targeting in the range of 85-89% did not affect severe ROP/death
- O_2 saturation targeting in the range of 85-89% resulted in a significant reduction in severe ROP (17.9 to 8.6%, NNT = 11)
- However, mortality was significantly increased in the 85-89% target group (19.9 versus 16.2%, NNH = 27)
- The mortality effect persisted to 18-22 months corrected age

BOOST II UK and Aus/NZ Trials Enrollment Stopped

"Preterm babies who were having their oxygen targeted to keep them in the range 91-95% were surviving more often than preterm babies who were having their oxygen targeted to keep them in the range 85-89%."

https://www.npeu.ox.ac.uk/boost

BOOST II UK and Aus/NZ Trials Enrollment Stopped

"The difference was so clear that it was extremely unlikely to change if the trial continued to the end."

"Because of this it was decided that no further babies should be entered into the trial and that babies currently in the trial should not continue in their allocated groups."

https://www.npeu.ox.ac.uk/boost

NeOProM

International collaboration on a prospective meta-analysis

Meta-analysis of SaO_2 Targets Trials
Death (latest age)

	Lower SaO_2	Higher SaO_2
SUPPORT	140/663	111/648
BOOST II	235/1221	202/1220
COT	97/584	88/577
	472/2439	409/2445
Risk increase 2.6%	19.3%	16.7%

RR 1.16 (1.03, 130) , p=0.018
NNH 38

Thanks to the many infants, parents, and NICU staff

Thanks to the members of the Neonatal Research Network

NICHD Neonatal Research Network Centers (2005-2009)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

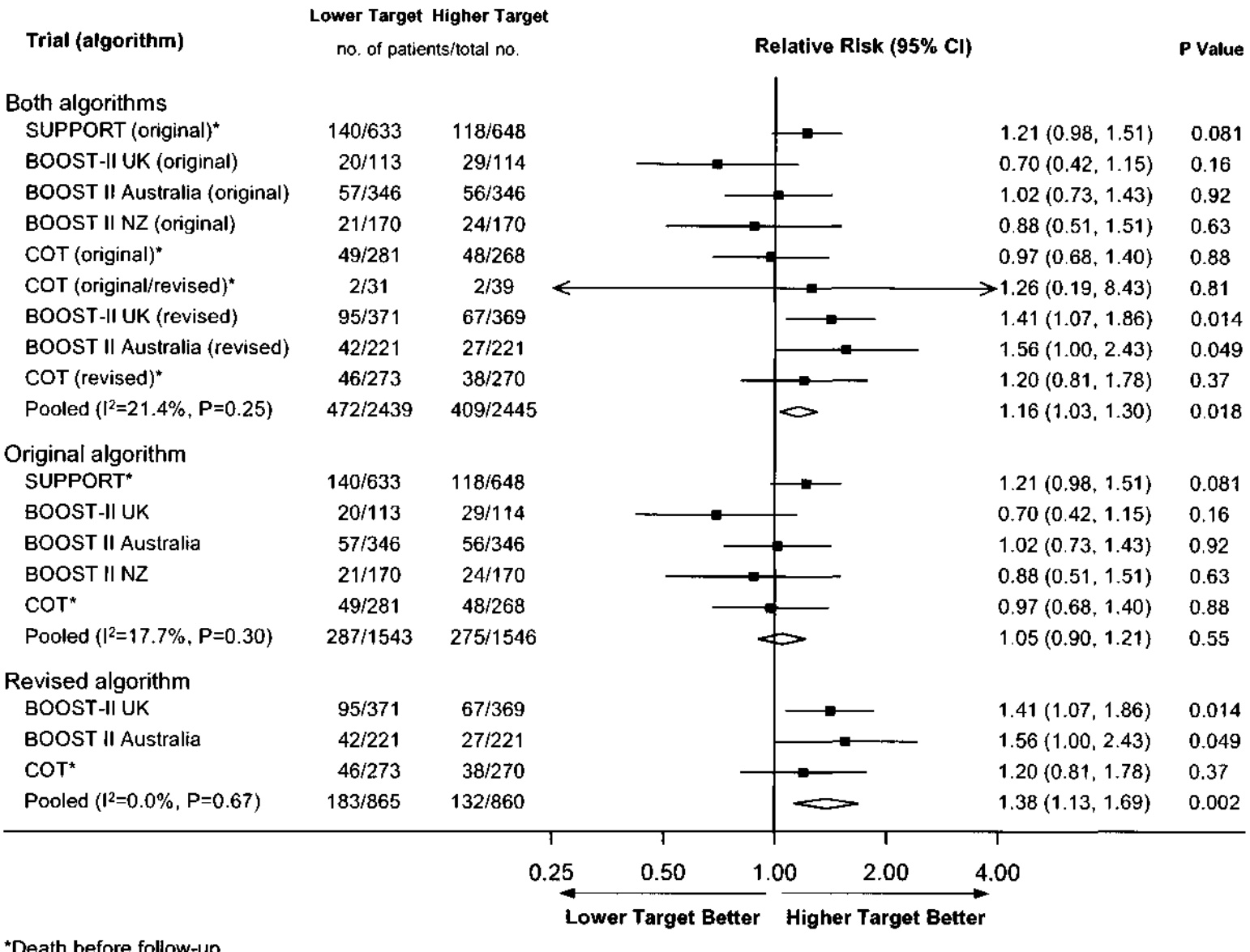
Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH & HUMAN SERVICES - USA

NeOProM trials

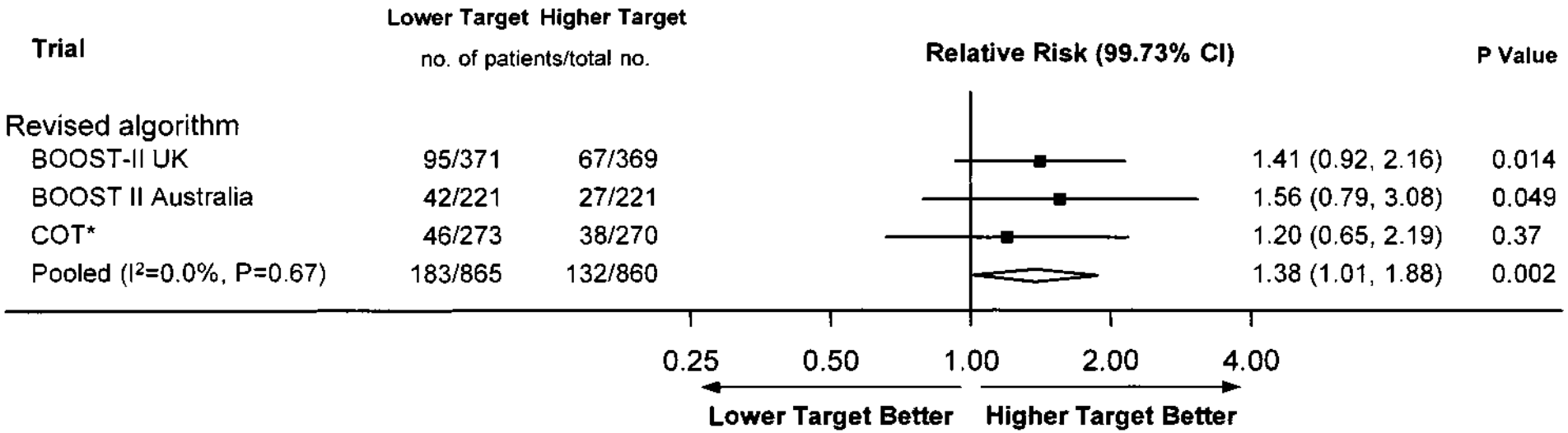
Death at discharge/before follow-up



*Death before follow-up

NeOProM trials

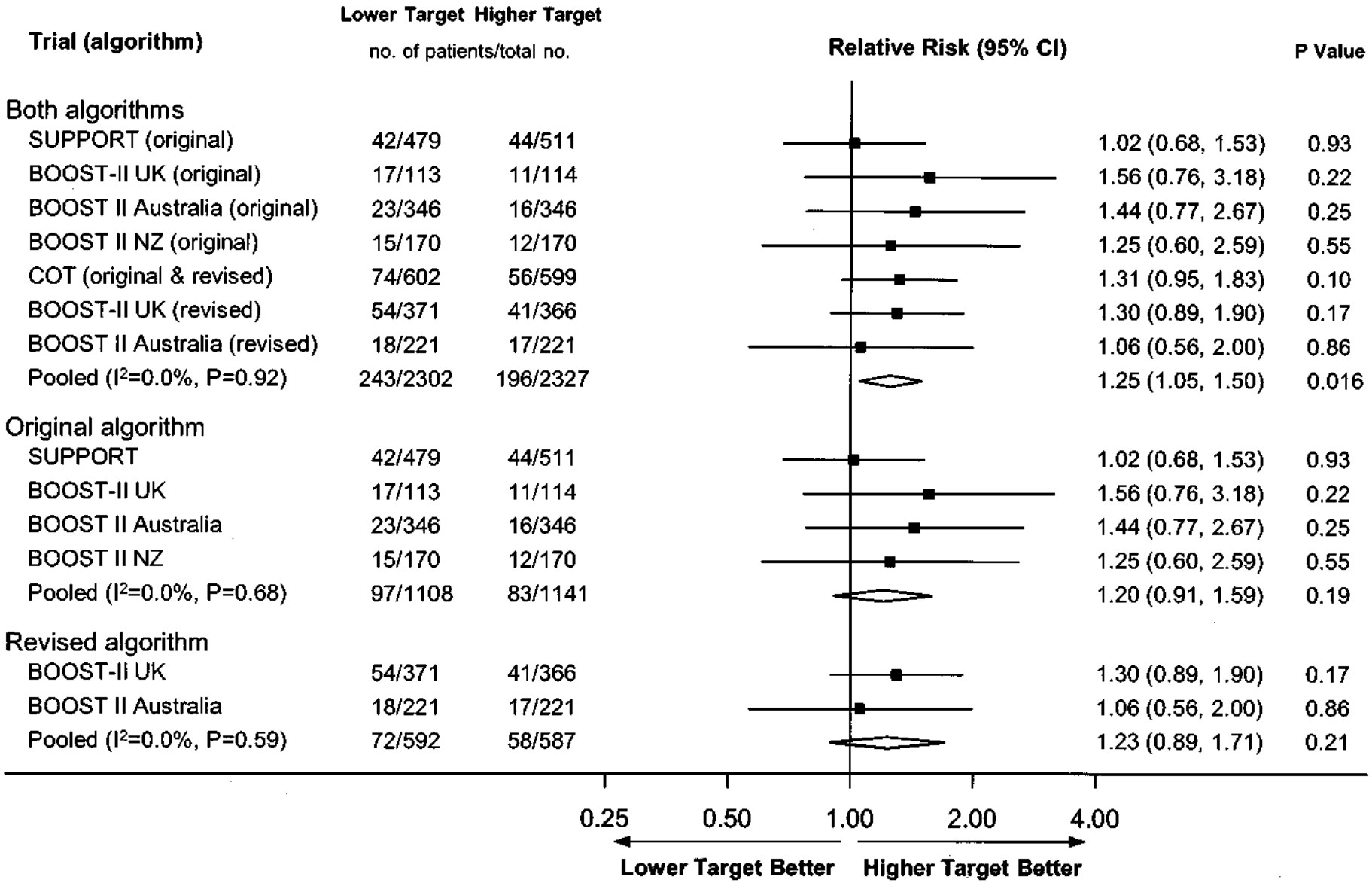
Death at discharge/before follow-up



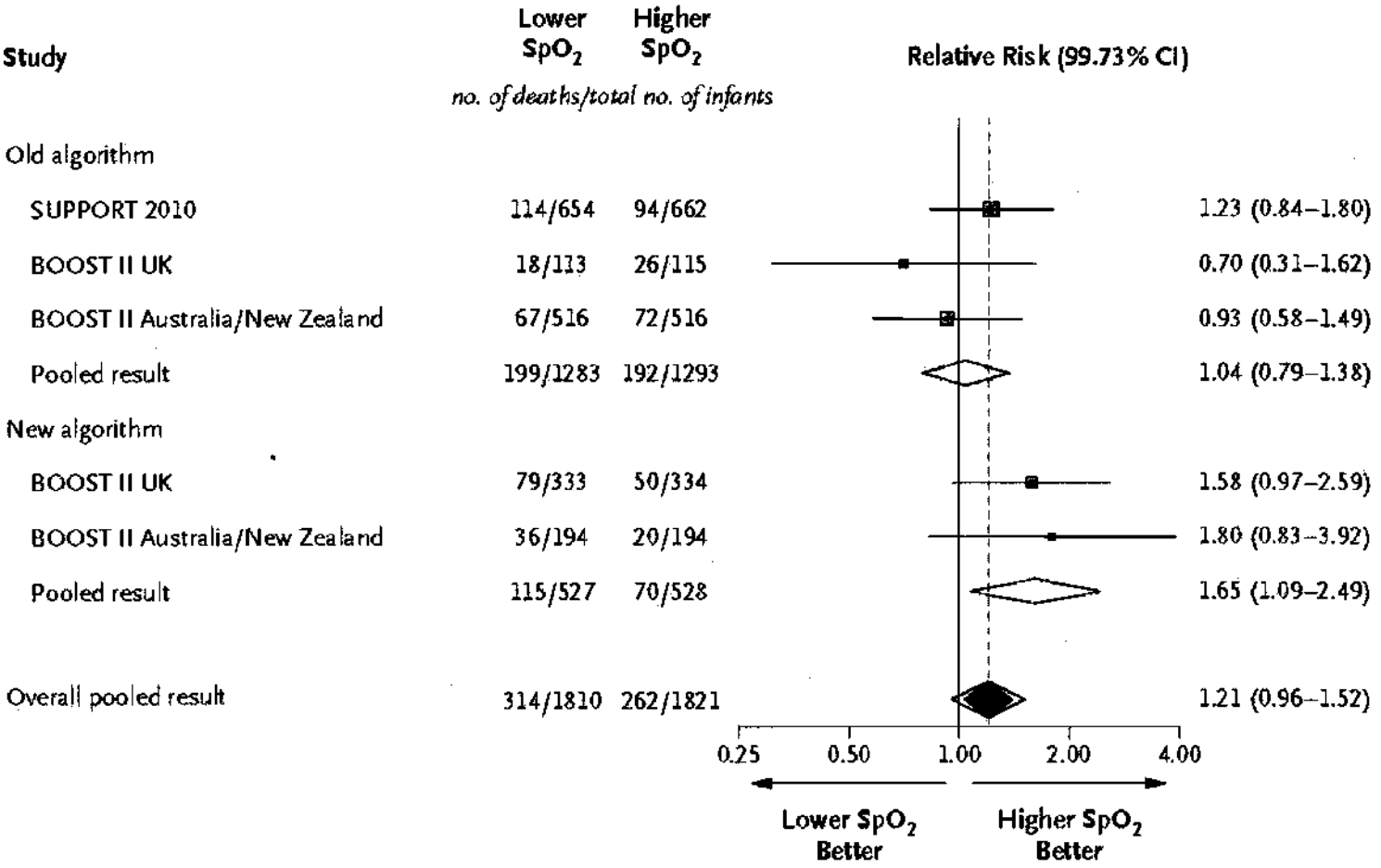
*Death before follow-up

NeOProM trials

Necrotising enterocolitis



Survival to 36 Weeks in 3631 Infants in the SUPPORT and BOOST II Trials



Stenson et al. N Engl J Med. 364:1680-2, 2011

Conclusions

- Lower oxygen saturation targeting (85-89%) decreases severe ROP
- Higher saturation targeting (91-95%) decreases mortality

Where Are We Now? Take Home Message

- Most current data suggest that oxygen saturation in the low 90s is sufficient to preterm infants
- Additional oxygen supplementation to keep O_2 saturations > 95% increases ROP and may worsen pulmonary outcomes
- Targeting O_2 saturations in the high 80s increases mortality
- Compliance with oxygen saturation targets can be improved

Where Are We Now? Consider Changes in Practice

- Target saturations 91-95%
- Develop guidelines and protocols to minimize hyperoxia
  1. High saturation alarm at 95% if the baby is on oxygen supplementation
  2. High saturation alarm at 99% if the baby is on room air, but at risk for getting oxygen supplementation (and not having saturations at 100%, obviously)
- saturations 91-95%
- Develop guidelines and protocols to minimize hypoxemia

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: FW: WF 322318 - FYI - SUPPORT Study
Date: Thursday, May 23, 2013 12:56:00 PM
Attachments: 322318 - Incoming - Control Sheet.pdf
322318 - Incoming - Source Doc email to Secretary.pdf
322318 - Incoming - Source Document.pdf
Importance: High

This was sent to us as an FYI only -

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From: Bock, Robert (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 12:49 PM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Pham, Luan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: WF 322318 - FYI - SUPPORT Study
Importance: High

From: Ott, Sandra (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 12:22 PM
To: Kaeser, Lisa (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: WF 322318 - FYI - SUPPORT Study

This has been assigned by OS to the Office of the Assistant Secretary and NIH as Information only. FYI copies have been sent to NICHD, OCPL, OER, and OSP. This was also sent as an FYI to Drs. Collins, Tabak, and Hudson. The PA on this is Lisa Marshall.

From: EDRMS_NO_REPLY@mail.nih.gov [mailto:EDRMS_NO_REPLY@mail.nih.gov]
Sent: Thursday, May 23, 2013 11:22 AM
To: Brown, Crystal (NIH/NICHD) [C]; Ott, Sandra (NIH/NICHD) [E]; Wood, Vandora (NIH/CIT) [C]
Subject: WF 322318 - Review FYI (CC)

To whom it may concern:

Message from the Director's Document and Records Management System (DDRMS)

You have received a task notification requiring your attention.

Additional instructions are included on the task form, please click the following link to open the task:

Note that we have implemented a temporary workaround for accessing tasks. Please click the following link and follow the instructions below:

Task

1. Login the system as you normally do.
2. You will see your "My Task" list.
3. Click the plus mark to the left of the "Work Queues" item in the left pane.
4. Click on your IC name in the left pane.
5. Locate the workfolder number indicated in the Subject field on this email.
6. Double-Click on the Workfolder and the task form will open.
7. Proceed as normal.

Please do not reply to this email, this is an automated message.

If you have concerns please contact the NIH Help Desk at (301) 496-4357.

Work Folder Information
Work Folder: WF 322318
Process: IC FYI - WF 322318
Program Analyst: Marshall, Lisa (NIH/OD) [E]
WF Subject: Report Prepared for the HHS Secretary from Public Citizen. Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure that Risks were Minimized. OS FYI only.
IC:NICHD
From: Carome, Michael;Wolfe, Sidney;Macklin, Ruth;
To: Sebelius, Kathleen;
Remarks: OS assigned to the Office of the Assistant Secretary and NIH as Info only. FYI to NICHD, OCPL, OER, and OSP. Also sent FYI to Drs. Collins, Tabak, and Hudson. Thanks, Lisa Marshall

Secretary's Correspondence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

OS#:	**051520131009**	*Date on Letter:*	**5/8/2013**
From:	**Carome, Michael (Public Citizen)** **Wolfe, Frank (Public Citizen)** **Macklin, Ruth (Oublic Citizen)**		
City/State:	**Washington DC**	*Date Received:*	**5/15/2013**
On Behalf Of:	**,**	*Type:*	**General Public**
Subject:	**[Similar Ref: 051320131090] - Forwards Public Citizen Report, 'Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure That Risks Were Minimized.'**		
Synopsis:			
Subject Tags:	**None**		

Assigned to:	**OASH**		
PC:	**Jamar Hawkins**	*Date Assigned:*	**5/16/2013**
Action Required:	**Info Only**	*Date Reassigned:*	
		Reply Due Date:	

Info Copies To:	**NIH**		
Interim (Y/N):	**No**	*Date Interim Sent:*	
Comments:			
File Index:	**PO-4**	*CCC:*	**Ottis Hamilton**

RECEIVED
May 20,2013 10:03:25 WS# 20
OSNUM: 052020131012
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

From: Michael Carome [mcarome@citizen.org]
Sent: Wednesday, May 08, 2013 7:59 AM
To: Sebelius, Kathleen (HHS/OS)
Cc: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Menikoff, Jerry (HHS/OASH); Borror, Kristina C (HHS/OASH); Koh, Howard (HHS/OASH)
Subject: Public Citizen's Report on the SUPPORT Study
Attachments: 130508_Public Citizen's SUPPORT Study Report With Cover Letter_FINAL.pdf

Dear Secretary Sebelius:

Attached please find a report from Public Citizen's Health Research Group regarding the lack of informed consent for the NIH-funded SUPPORT study involving extremely premature infants. The original hardcopy of our report will follow by regular mail.

Thank you for your attention to this important matter.

Sincerely,

Michael A. Carome, M.D.
Deputy Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

From: Sarah Sorscher [ssorscher@citizen.org]
Sent: Monday, April 22, 2013 4:32 PM
To: Hamburg, Margaret A. (FDA); Woodcock, Janet (FDA/CDER)
Cc: Sebelius, Kathleen (HHS/OS); Sidney Wolfe; Michael Carome
Subject: Request For Explanation on Delay - Balanced Solutions Recall
Attachments: Request For Explanation on Delay - Balanced Solutions Recall.pdf

Dear Drs. Hamburg and Woodcock,

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, writes you to request an explanation for the unacceptable one-month delay between the Food and Drug Administration's inspection of Axium Healthcare Pharmacy (dba Balanced Solutions Compounding Pharmacy), finished on March 15, 2013, and the subsequent nationwide voluntary recall of all lots of sterile products compounded by this pharmacy.

Please view the attached pdf for a full explanation of our request.

Sincerely,
Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

Michael Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

*** RECEIVED ***
May 20,2013 10:03:25 WS# 20
OSNUM: 052020131012
OFFICE OF THE SECRETARY
CORRESPONDENCE

FDA inspectors visited Balanced Solutions Compounding Pharmacy between March 12 and 15, 2013, and observed black particles in seven vials of "sterilized" triamcinolone acetonide injectable solution and a cloth-like filament in one vial of "sterile" chromium chloride injectable solution. These eight contaminated vials were taken from two production lots that had previously been "released and distributed."[2] The FDA analyzed a sample of chromium chloride and identified gram negative bacteria in the product.

FDA inspectors also identified unsanitary conditions during the inspection, raising concerns that quality-control processes were inadequate and product sterility may have been compromised. These conditions included spills and splatters of white, amber, and clear residue in the ISO 5 "clean" room. One of the splatters was a patch of white residue approximately one foot in diameter on an air guard behind the table on which sterile injectable drugs were being prepared. Inspectors also found cracked and peeling paint; inadequate air filters; inadequate procedures and monitoring to prevent and detect microbial contamination; inappropriate, nonsterile clothing worn by personnel for sterile drug processing; and what appeared to be brown rust in the room in which these personnel got dressed.

The April 17, 2013, recall was issued more than a month after inspectors visited Balanced Solutions Compounding Pharmacy. During that time, doctor's offices and patients nationwide continued to use products that had been prepared at the pharmacy under unsanitary conditions.

Prior to the April 17 recall, Balanced Solutions Compounding Pharmacy issued a partial recall that covered the chromium chloride that had been sampled and was found to contain gram negative bacteria.[3] To date, the company has received no reports of injury or illness associated with the recalled products.

We write to request an explanation for the FDA's delay in taking prompt action to protect public health. We also seek answers to the following specific questions:

1. During the March 12-15 inspection of Balanced Solutions Compounding Pharmacy, FDA inspectors identified visible contamination in eight vials of "sterilized" injectable drugs that already been released and distributed. Sometime thereafter, the company issued a partial recall that covered the samples of chromium chloride known to have been contaminated. Why did the FDA fail to warn health care providers against these sterile products and issue a public alert at this time?
2. During the March 12-15 inspection of Balanced Solutions Compounding Pharmacy, FDA inspectors identified unsanitary conditions and numerous other safety concerns. Given that multiple products distributed nationwide were prepared under these unsanitary conditions, why did the FDA fail to issue an immediate press release warning health care providers and the public of the risk of contamination?

[2] 483 Inspection Report. Axium Healthcare Pharmacy dba Balanced Solutions Compounding. http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM345694.pdf. Accessed April 22, 2013.

[3] Axium HealthCare. Balanced Solutions Compounding Pharmacy, LLC, announces a voluntary nationwide recall of all sterile compounded products due to a lack of sterility assurance. http://www.axiumhealthcare.com/aboutUs/newsRoom/59.pdf. Accessed April 22, 2013

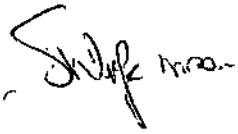
3. Why did a full month pass between the time of the inspection and the time of the first public recall of products from Balanced Solutions Compounding Pharmacy?
4. Between March 15 and April 17, how many different kinds of sterile compounded products were produced and distributed from Balanced Solutions Compounding Pharmacy, and what was the volume of products produced?
5. Has the FDA granted approval for any of the drugs produced at Balanced Solutions Compounding Pharmacy?
6. Has Balanced Solutions Compounding Pharmacy demonstrated that all of the products produced at the pharmacy are compounded only upon receipt of a valid prescription order?

Thank you in advance for your attention to this important matter.

Sincerely,

Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

Michael Carome, M.D.
Deputy Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

cc: The Honorable Kathleen Sebelius, Secretary of Health and Human Services

Report Prepared for
Secretary of Health and Human Services Kathleen Sebelius

Analysis of the Complete Protocol and Consent Form for the SUPPORT Study: Lack of Informed Consent and a Failure to Ensure That Risks Were Minimized

May 8, 2013

Michael Carome, M.D.
Sidney Wolfe, M.D.
Ruth Macklin, Ph.D.

www.citizen.org

About Public Citizen

Public Citizen is a national nonprofit organization with more than 300,000 members and supporters. We represent consumer interests through lobbying, litigation, administrative advocacy, research, and public education on a broad range of issues, including consumer rights in the marketplace, product safety, financial regulation, safe and affordable health care, campaign finance reform and government ethics, fair trade, climate change, and corporate and government accountability.

About Ruth Macklin

Ruth Macklin is Professor (Bioethics) in the Department of Epidemiology & Population Health at Albert Einstein College of Medicine in Bronx, NY. She is Director, Training Program in Research Ethics in the Americas, sponsored by the NIH Fogarty International Center. She also is on the Board of Directors and is Past President of the International Association of Bioethics.

Contents

I. Background

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), funded by the National Institutes of Health (NIH), involved 1,316 extremely premature infants enrolled between 2005 and 2009 at more than 20 prominent medical research centers throughout the U.S.[1] The infants in the study were born at approximately 24 to 28 weeks gestation and weighed an average of less than two pounds.[2] The research centers that participated in the SUPPORT study are part of a multi-institution group known as the Neonatal Research Network (NRN), which was established in 1986 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development to conduct research studies on preterm and term newborns.

The SUPPORT study involved two simultaneous experiments. In one experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing (ventilation of the lungs) following delivery.[3] Babies in one group were treated with a face mask, called a continuous positive airway pressure (CPAP) mask, to deliver pressurized air supplemented with oxygen; in this group (**CPAP group**), the babies breathed on their own. Babies in the other group were intubated (underwent an invasive procedure involving insertion of a tube inserted into the trachea, the main airway leading to the lungs); given the drug surfactant, which helps the lungs stay open; and placed on mechanical ventilation (an artificial breathing machine; **mechanical-ventilation group**).

For the other, simultaneous experiment, which is the primary focus of this report, babies assigned to both the CPAP and mechanical-ventilation groups were further randomly divided between a low-oxygen group and a high-oxygen group.[4] For the low-oxygen group, the SUPPORT study investigators tried to maintain the babies' blood oxygen levels in a low target range (oxygen saturation level of 85 to 89 percent), and for the high-oxygen group in a high target range (oxygen saturation level of 91 to 95 percent), rather than adjust each baby's oxygen levels within the broader range of 85 to 95 percent to meet his or her individual needs, as would have been the case if the baby had not been in the study. The researchers then measured the impact of the two target ranges of oxygen levels for premature babies – specifically, whether infants in one group were more likely to die, suffer brain damage, or develop an eye disease called retinopathy of prematurity and blindness in comparison to the other group.

In 2011, the Office for Human Research Protections (OHRP) — a regulatory office within the Department of Health and Human Services (HHS) Office of the Secretary that is charged with enforcing the HHS human subjects protection regulations at 45 C.F.R. Part 46 — opened a compliance oversight investigation of the SUPPORT study, apparently after receiving allegations that the study violated provisions of these regulations.[5] On March 7, 2013, OHRP sent a

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[1] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.
[2] *Ibid.*
[3] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.
[4] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.
[5] Office for Human Research Protections. Letter to the University of Alabama at Birmingham. March 7, 2013. http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf. Accessed April 24, 2013.

compliance oversight determination letter to the University of Alabama at Birmingham (UAB) — the lead institution for the oxygen experiment component of the SUPPORT study — stating that the "the [consent forms] for this trial failed to adequately inform parents of the reasonably foreseeable risks and discomforts of research participation." In particular, OHRP noted that the UAB IRB-approved consent forms signed by parents of babies who enrolled in the study failed to explain that:[6]

(1) The study involved substantial risks, and there was significant evidence from past research indicating that the level of oxygen provided to a premature baby can have an important effect on many outcomes, including whether the baby could become blind, develop serious brain injury, and even possibly die;

(2) By participating in this study, the level of oxygen a baby received would in many instances be changed from what they would otherwise receive;

(3) Some babies would receive more oxygen than they otherwise would have, in which case, if the researchers were correct in how they supposed oxygen affects the eyes, those infants would have a greater risk of going blind; and

(4) The level of oxygen being provided to some babies, compared to the level they would have received had they not participated, could increase the risk of brain injury or death.

In its March 7 letter, OHRP noted that the agency had reviewed the consent forms approved by the IRBs for all SUPPORT study institutions and had found problems with all of them similar to those described above.[7] However, OHRP only required that UAB submit a plan to ensure that IRB-approved consent forms include and adequately address all elements of informed consent required under the HHS human subjects protection regulations.

On April 10, 2013, Public Citizen wrote to Secretary of Health and Human Services Kathleen Sebelius, expressing concern that OHRP did not go far enough in its determinations of noncompliance and in the scope of its required action.[8] While agreeing with OHRP that the SUPPORT study consent forms failed to disclose the substantial risks of the research, Public Citizen asserted that based on the information presented in OHRP's letter, the agency should have found that the UAB IRB-approved consent form failed to disclose one key purpose of the research — to see whether babies were more likely to die in the low- or high-oxygen group — and failed to identify as experimental the procedures for targeting the low and high oxygen saturation targets and explain how these procedures compared to the usual standard of care for managing oxygen therapy in premature babies not involved in the study. Public Citizen also stated that OHRP should have required that all NRN institutions that conducted the SUPPORT study take corrective actions to address the serious deficiencies in the consent forms.

---

[6] *Ibid.*
[7] *Ibid.*
[8] Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT Study. April 10, 2013. http://www.citizen.org/documents/2111.pdf. Accessed April 24, 2013.

Finally, Public Citizen urged in its April 10 letter that the Secretary, along with NIH Director Francis Collins, personally apologize to the parents of the 1,316 babies enrolled in the SUPPORT study and divulge to them the information previously not disclosed regarding the purpose, nature, and risks of the experiment.

Following widespread media attention about OHRP's March 7 letter to UAB and Public Citizen's April 10 letter to the Secretary, the SUPPORT study investigators and others have issued numerous public statements defending the conduct of the study and the adequacy of the informed consent process.

As of the April 10 letter, Public Citizen only had access to very limited excerpts from the SUPPORT study protocol and from the UAB IRB-approved consent form that were presented in OHRP's March 7, 2013, letter to UAB, as well as published reports in the medical literature communicating the results of the study[9,10,11] and the abbreviated study description posted on the ClinicalTrials.gov website.[12] Since April 10, we have obtained additional relevant information about the SUPPORT study following the recent public release of the complete protocol and the complete UAB IRB-approved consent form. Public Citizen also has just obtained from NIH, under a Freedom of Information Act request, SUPPORT study consent forms that were approved by 21 other IRBs (see the Appendix for the complete list of institutions).[13] This report provides Public Citizen's analysis of these complete documents, as well as responses to numerous statements issued by the SUPPORT study investigators and others attempting to defend the conduct of this study and the adequacy of the informed consent process.

II. Analysis of new information gleaned from the complete SUPPORT study protocol and the IRB-approved consent forms

A. Neonatal intensive care unit (NICU) medical teams caring for critically ill premature babies were intentionally provided with inaccurate oxygen saturation levels

The most disturbing finding from our review of the newly available information was the failure of half of the IRB-approved consent forms to disclose to the parents of the subjects the experimental procedure, under which the entire medical team caring for each premature baby in the study was intentionally given inaccurate information about the baby's blood oxygen saturation levels by using pulse oximeters miscalibrated across the wide range of oxygen saturations between 85% and 95%. Of note, oxygen saturation measured by a pulse oximeter is a clinical parameter of such importance in monitoring critically ill patients that it is sometimes

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[9] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.
[10] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.
[11] Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med.* 2012;367(26):2495-2504.
[12] ClinicalTrials.gov. Surfactant positive airway pressure and pulse oximetry trial (SUPPORT); ClinicalTrials.gov identifier: NCT00233324. http://clinicaltrials.gov/ct2/show/NCT00233324. Accessed March 28, 2013.
[13] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed May 7, 2013.

referred to as the "fifth vital sign" (the first four vital signs being pulse, blood pressure, breathing rate, and temperature).[14]

Equally disturbing is our finding that *none* of the IRB-approved consent forms disclosed the dangers posed to the babies by giving the entire medical team such intentionally inaccurate information about their oxygen saturation levels.

This experimental procedure is explained in the following excerpts from the protocol:[15]

> (Page 12, section 3.7, Randomization) The Pulse Oximeters (PO) will have unique identifying labels and the oximeter specified in the randomization will be identified by a unique number which will match the number of the study Pulse Oximeter assigned for that infant. **All caretakers including the coordinators will be blinded to the [actual] Pulse Oximeter Range**... [Emphasis added]
>
> (Page 17, 4.1 B Study Intervention: Low versus High SpO2 Range) There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) are described below, and will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. See below for further explanation. This deviation is similar to the BOOST trial which used a continuous 3% offset. As an added safety feature, the POs used in this trial will revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

The following table[16] reveals the displayed (i.e., intentionally inaccurate) oxygen saturation levels relative to each actual oxygen saturation level between 85% and 95% for infants in both the high-oxygen and low-oxygen groups:

[14] Neff TA. Routine oximetry: A fifth vital sign. *Chest.* 1988;94(2):227.
[15] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed April 24, 2013.
[16] The table was constructed by extracting data from Table 1 on page 17 of the complete protocol and from the unnumbered figure on page 18 of the protocol.

Table: Actual and inaccurately displayed oxygen levels in high- and low-oxygen-group babies

Displayed for high oxygen group (intentionally low)	84%	85%	85%	85%	85%	86%	87%	88%	89%	90%	92%	92-94%	96%
Actual	**84% *(Alarm)***	**85%**	**86%**	**87%**	**88%**	**89%**	**90%**	**91%**	**92%**	**93%**	**94%**	**95%**	**96% *(Alarm)***
Displayed for low oxygen group (intentionally high	84%	86-88%	88%	90%	91%	92%	93%	94%	95%	95%	95%	95%	96%

Note that for any displayed oxygen saturation level between 88% and 92%, the absolute difference between the actual oxygen saturation levels for the high- versus low-oxygen groups was 5% to 6%. For example, when the *displayed* oxygen level was 90%, the *true* oxygen level was 93% for the high-oxygen group and 87% for the low-oxygen group.

In addition, for the high-oxygen group, a *displayed* oxygen saturation level of 85% meant the *actual* level was anywhere between 85% and 88%, whereas for the low-oxygen group, a *displayed* oxygen saturation level of 95% meant the *actual* level was anywhere between 92% and 95% (in both cases, the actual value was unknown to the medical teams caring for these babies). These differences in the actual saturation levels between groups for any given inaccurately displayed level, particularly the 5% to 6% between-group differences for the displayed range of 88% to 92%, represented clinically important differences in the babies' actual blood oxygen content. Such differences certainly could have adversely impacted the management decisions that were being made by the medical teams caring for the babies in the SUPPORT study.

Because of the inaccurately high oxygenation saturation values provided to the medical team by the pulse oximeters for babies in the low-oxygen experimental group, it is plausible that the medical team may have treated some critically ill babies with too little oxygen, potentially resulting in brain injury and death secondary to hypoxemia (deficient oxygen). In contrast, because of the inaccurately low oxygenation saturation values provided to the medical team by the pulse oximeters for babies in the high-oxygen experimental group, it is also plausible that the medical team may have treated those babies with more oxygen than they needed, resulting in severe retinopathy of prematurity, requiring surgery and possibly causing blindness. What we do not know because the study lacked a usual standard of care control group, but suspect, is that if the medical teams had been given the correct information about oxygen saturation levels and these babies had been treated based on their individual needs as per current routine standard of practice, some deaths might have been prevented in the low-oxygen group, and some cases of severe retinopathy might have been prevented in the high-oxygen group.

B. Half of the IRB-approved consent forms did not disclose the experimental procedure for intentionally providing the NICU medical teams with inaccurate oxygen saturation levels, and none disclosed the risks of this procedure

To our dismay, half (11) of the 22 IRB-approved consent forms for the SUPPORT study did not disclose to the parents that if they enrolled their babies in this experiment, their babies' entire medical team would be intentionally given inaccurate information about the babies' oxygen saturation levels.[17] Also, none of the consent forms described how this experimental procedure could have impacted important clinical decisions related to the babies' care.[18] This protocol-specified procedure was a clear departure from the standard of care that these critically ill babies would have received had they not been enrolled in the study. Moreover, the protocol offered no evidence that this experimental approach was safe. Indeed, routinely providing the entire medical team with inaccurate information about blood oxygen saturation levels, a critically important clinical parameter monitored in these premature babies, may well have exposed these babies to potentially serious, life-threatening risks. This experimental procedure presented important additional risks beyond those associated with attempting to confine the premature babies' oxygen saturation levels to either a high- or low-oxygen range. No such risks were described in any of the IRB-approved consent forms. In fact, at least three of the consent forms, including the form approved by the UAB IRB, made the following extraordinarily misleading statement:[19]

> "There is no known risk to your baby from monitoring with the pulse oximeters used for this study."

Many other IRB-approved consent forms made statements like the following:[20]

> "Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant."

Understanding the clinical importance of oxygen saturation levels in the routine management of premature babies is essential for recognizing the serious risks of providing protocol-specified misinformation to the NICU medical teams that cared for the infants in the SUPPORT study. These risks become apparent when one considers the protocol-specified criteria that were used to make decisions about whether these babies should be intubated and placed on mechanical ventilation or extubated if they were already on a ventilator. To understand these criteria, it is important to first remember that the SUPPORT study included a second simultaneous experiment, in addition to the experiment testing differences in oxygen saturation target ranges, in the same 1,316 babies enrolled in the study. For this second experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing following delivery. Babies in one group were treated with a face mask, called a CPAP mask, to deliver pressurized air supplemented with oxygen; in this group, the babies breathed on their own. Babies in the other group were intubated; given the drug surfactant, which helps the

[17] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed May 7, 2013.
[18] *Ibid.*
[19] *Ibid.*
[20] *Ibid.*

lungs stay open; and placed on mechanical ventilation. Babies assigned to each of these two groups were further randomly assigned to the low-oxygen group or the high-oxygen group.

Because the investigators recognized that some babies assigned to the CPAP group might not have been able to sustain adequate breathing on their own, the protocol specified rescue criteria that allowed the medical team to intubate the baby and place him or her on a ventilator. The oxygen saturation level measured by an intentionally inaccurate pulse oximeter was one such criterion. This is described in the following excerpt from the protocol:[21]

> (Page 14, under heading "NICU Management") [The babies assigned to the CPAP group] *MAY* be intubated if they meet ***ANY of*** the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant
>
> **Intubation:**
> - An FiO_2 >.50[22] required to maintain an indicated [oxygen saturation level] ≥ 88% (using the altered Pulse Oximeters) for one hour... [Emphasis in original]

Like the medical decision regarding intubation of study babies, the protocol also stipulated that for a CPAP-group baby who *had been intubated*, the medical team must attempt to extubate the baby based on criteria that included a protocol-specified threshold oxygen saturation level of 88%:[23]

> (Page 14, under the heading "Extubation") An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if* **ALL** *of the following criteria are met and documented on a single blood gas*
>
> - PaCO2 < 65 torr with a pH > 7.20 (arterial or capillary samples)
> - An indicated SpO2 ≥ 88% with an FiO2 ≤ 50%
> - A mean airway pressure (MAP) < 10 cm H2O, ventilator rate ≤ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
> - Hemodynamically stable…
> - Absence of clinically significant PDA
>
> [Emphasis in original]

The protocol further specified that use of these criteria for intubation and extubation decisions were to continue for the first 14 days of life.

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[21] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed April 24, 2013.

[22] FiO_2 means the fraction of inspired oxygen, which is the oxygen composition of the inspired air. Room air has an FiO_2 of .21 (21% oxygen). The FiO_2 can be increased to a maximum of 1.00, which would be 100% oxygen.

[23] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed April 24, 2013.

The fact that the protocol-specified criteria for making the crucial medical decisions regarding whether to intubate or extubate critically ill premature babies were based on oxygen saturation levels, as measured by a pulse oximeter, is important for two reasons. First, it underscores the vital importance of the actual, real oxygen saturation levels in the hour-to-hour management of FiO2s settings (the level of supplemental oxygen), mechanical ventilation treatments, and many other clinical decisions in critically ill premature babies.

Second, and more relevant to the babies who were enrolled in the SUPPORT study, the intentional provision of inaccurate oximetry information to the medical teams caring for these babies posed significant risks for these babies. For example, the inaccurate oxygen level readings could have led the medical teams to intubate and artificially ventilate some babies who did not need to undergo these medical procedures, thus unnecessarily exposing the babies to the risks of intubation and mechanical ventilation. On the other hand, the inaccurate oxygen level readings could have led the medical teams to *not* intubate and mechanically ventilate other babies who did need these medical procedures, thus exposing them to risks of inadequate oxygen delivery.

The risks of intentionally providing the medical teams with *inaccurate* oxygen saturation levels are best understood by considering how this inaccurate data, combined with the protocol-specified criteria for intubating or extubating CPAP-group babies — criteria presumably based on *accurate* oxygen saturation levels in the setting of routine standard of care — could have altered the care of a baby assigned to the high-oxygen group versus a baby assigned to the low-oxygen group.

First consider a baby in the CPAP group who was randomly assigned to the high-oxygen target range and therefore had not been intubated. Let us suppose the baby, during the first day of life, needed an FiO_2 of 0.55 to breathe in order to maintain an oxygen saturation level of 88% as *inaccurately displayed* on the miscalibrated pulse oximeter. The baby really would have had an *actual* oxygen saturation level of 91%. If the medical team had had an *accurate* pulse oximeter reading of 91%, the team likely would have lowered the FiO2 to 0.50. If the baby's actual oxygen saturation level subsequently remained at or above 88%, the baby would not have needed to be intubated. However, because the medical team received only the inaccurate pulse oximetry reading of 88%, the team could well have decided, under the protocol-specified rescue criteria for babies in the CPAP group, to intubate the baby and start mechanical ventilation when it likely was not clinically necessary. This could have unnecessarily exposed some high-oxygen group babies to increased risk of: (a) trauma to the mouth and gums during intubation; (b) trauma to the trachea, resulting in bleeding and puncture of the airway during intubation; (c) pneumothorax (collapsed lungs, possibly resulting in the need for insertion of chest tubes); (d) pneumonia during mechanical ventilation; and (e) death. If the now inappropriately intubated baby survives to be subsequently extubated, the same circumstances that led to the first inappropriate intubation could recur, leading to a second inappropriate intubation and unnecessary exposure again to the same risks.

Now consider a second baby in the CPAP group who was randomly assigned to the low-oxygen target group. Let us suppose the baby, during the first day of life, maintained an *inaccurate* oxygen saturation level displayed as 88% on the miscalibrated pulse oximeter while breathing an FiO_2 of 0.50. In reality, the baby *actually* would have had an oxygen saturation level of 85% to

86%, already below the threshold that should have triggered rescue intubation and mechanical ventilation. If the medical team had had an *accurate* pulse oximeter reading, the team likely would have raised the FiO_2 above 0.50 to try to increase the oxygen saturation level. If after one hour, the *actual* oxygen saturation remained at or below 88% on the higher FiO_2, the baby likely could have been intubated. However, because the medical team received only the inaccurate pulse oximetry reading of 88%, clinically indicated intubation of the baby may have been delayed. Inappropriate delays in making necessary changes in care, including making adjustments in the FiO2 and performing clinically indicated intubation, could have unnecessarily exposed some babies in the low-oxygen group to increased risk of prolonged hypoxemia with inadequate oxygen delivery to the brain, resulting in neurological damage and possibly death.

Finally, continuing one step further with the example of the baby in the low-oxygen group, let us suppose this baby was finally intubated when the *inaccurately* displayed oxygen saturation level fell to 85% for more than one hour while breathing on an FiO_2 of 0.55. Inappropriate extubation subsequently could have occurred *too soon* when the *inaccurately* displayed oxygen saturation level increased to greater than 88% on the miscalibrated pulse oximeter while the baby was on an FiO_2 less than 0.50 (with all other criteria for extubation met), when in fact the *actual* oxygen saturation level was 85% to 86%. Like the first example, this sequence could have repeated itself leading to a second inappropriately delayed intubation followed by another too-soon extubation.

Remarkably, the following statement from the protocol indicates that the investigators were well aware that the criteria of intubating and extubating the babies in the CPAP group, in the context of inaccurate oxygen saturation reading, could lead to inappropriate intubations and extubations and must have understood the risks:[24]

> (Page 15, under the heading "D/C CPAP) *CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.* [Emphasis in original]

It is truly disturbing that the investigators failed to clearly describe in the protocol and the consent forms the potential for both (a) protocol-driven intubations and extubations that *would not be* clinically indicated; and (b) protocol-driven delays in intubations or extubations that *would be* clinically indicated, as well as the risks of such protocol-driven events related to the oxygen experiment in the SUPPORT study. Equally disturbing is the apparent failure of the reviewing IRBs to recognize these risks.

C. None of the 22 IRB-approved consent forms disclosed that the high-oxygen saturation target was considered "more conventional" by the investigators, despite this being stated in the protocol

Another disturbing revelation gleaned from the just-released SUPPORT study protocol is the following summary statement of the oxygen experiment design:[25]

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[24] *Ibid.*
[25] *Ibid.*

> (Page 9, section 2.1, Study Design) 2) A prospective comparison of a lower SpO2 range (85% to 89%) with a **higher more conventional SpO2 range (91% to 95%)** until the infant is no longer requiring ventilatory support or oxygen. [Emphasis added]

Thus, the IRBs were informed by the investigators that the high-oxygen saturation target range was considered to be "more conventional" treatment for premature babies receiving routine standard of care, which implicitly means that the low-oxygen saturation target range was more unconventional. This characterization of the relative difference between the low and high oxygen targets used in the two experimental oxygen groups is in clear conflict with the following misleading statement presented to parents of the premature babies in the UAB IRB-approved consent form, which implied that both the low and the high range were equally conventional:[26]

> The babies in the lower range group will have a target saturation of 85-89%, while the babies in the higher range group will have a target saturation of 91-95%. **All of these saturations are considered normal ranges for premature infants.** [emphasis added]

Similar statements were made in the consent forms approved by IRBs at nearly all of the other participating institutions.

Two consent forms appeared to suggest that oxygen saturation ranges other than the two target ranges used in the SUPPORT study were most commonly used. For example, the IRB-approved consent form for Duke University Health System (DUHS) noted that the "aim in many units is to keep oxygen saturations between 88 and 92%," although it did not explain whether this was the case at DUHS.[27] Likewise, the IRB-approved consent form for Tufts Medical Center stated that at "Tufts Medical Center oxygen saturation is kept between 88-94%."[28] Disclosures of the oxygen saturation ranges most commonly targeted when caring for premature babies, such as the statement made in the Tufts Medical Center IRB-approved consent form, should have been made in the consent forms for all SUPPORT study institutions.

To summarize the deficiencies in the SUPPORT study consent process, the information now available from the complete SUPPORT study protocol and the IRB-approved consent forms demonstrates that parents gave consent for their babies to be enrolled in the SUPPORT study based on misleading information and without being provided with critically important information about the purpose, nature, and risks of this complex oxygen experiment.

D. The SUPPORT study protocol omitted critically important information necessary for understanding the full range of risks of the study and for assessing whether the risks to the subjects would be minimized

Finally, it is important to recognize the essential information that was *not* included in the full SUPPORT study protocol.

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[26] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed May 7, 2013..
[27] *Ibid.*
[28] *Ibid.*

First, the protocol lacked a robust, detailed explanation of the usual standard of care regarding such critical issues as the individualized adjustment of FiO_2 and decisions about intubation, extubation, and mechanical ventilation in critically ill premature infants at the NRN medical centers. For example, the protocol should have described in detail the clinical factors taken into account by expert neonatologists at these centers when making individualized decisions to adjust FiO_2 in extremely premature newborns. The protocol also should have described the criteria under the usual standard of care for making decisions about intubation, extubation, and mechanical ventilation, including the role of actual oxygen saturation levels. Without such information, it was not possible for the IRBs that approved this experiment to determine whether risks to the babies were minimized given: (a) the complexity of usual medical care in the NICU setting, (b) the added complexity of the experimental interventions in the study, and (c) the interactions between (a) and (b).

Second, the protocol failed to indicate whether it was ever standard of care at *any* participating NICU to routinely attempt to maintain the oxygen saturation levels for all extremely premature babies, regardless of their clinical status, within the range of 85% to 89%, and if so, how frequently this was the case. This information was particularly relevant to understanding the risks of the research and whether they were minimized because the investigators had indicated that the oxygen saturation target range of 91% to 95% was the "more conventional" of the two target oxygen saturation ranges being tested. This important acknowledgement by the investigators warranted further explanation. Of concern, the protocol offered no evidence that before developing the protocol, the SUPPORT study investigators had conducted a systematic survey of previous medical records of NICU babies in order to document current routine standard of practice for managing oxygen treatment in premature babies within their own NICUs.

Third, given the complexities of routine medical management of extremely premature infants and the interaction between the different complex experimental interventions of the SUPPORT study, the minimization of the risks to babies enrolled in the study would have required a detailed plan for unblinding the NICU medical teams when the masking procedure using intentionally miscalibrated pulse oximeters posed a threat to the health of the babies. The complete SUPPORT study protocol lacked such a detailed plan.

Fourth, because (a) the oxygen experiment involved only two experimental groups and no control group, and (b) the primary efficacy endpoint was a composite of the two competing harms of death and retinopathy, adequate safety monitoring would have required periodic checking for differences between the low-oxygen and high-oxygen groups for both death and retinopathy *separately*. This is reflected in the way the results were presented in the published paper.[29] According to the protocol, death was monitored as an adverse event, but retinopathy was not. The IRBs that reviewed and approved the study did not appear to understand the complexities of the oxygen experiment component of the SUPPORT study and the off-setting risks involved, and as a result, they were unable to determine whether the monitoring plan was sufficient to ensure the safety of the babies and minimize risks to them.

[29] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.

For example, retinopathy should have been monitored as an adverse event and monitored closely. For the low-oxygen group babies, death was a risk and was monitored. For the high-oxygen group babies, retinopathy was the risk and should have been monitored as an adverse event, but the protocol safety monitoring plan did not indicate that it was. Because retinopathy, part of the primary composite efficacy endpoint, often requires surgery and can lead to blindness, it represented a clear potential harm to the babies of significant enough degree to require monitoring. The study demonstrated that the high-oxygen group babies had a highly significant increase in retinopathy in comparison to the low-oxygen group babies ($p<0.001$).[30] If the incidence of retinopathy had been monitored separately as an important adverse event in the high-oxygen group at increased risk for this adverse outcome and compared to the incidence in the low-oxygen group, a recommendation to stop the trial early probably could have been made by the data and safety monitoring board, potentially saving lives in the low-oxygen group due to hypoxemia and decreasing the need for retinal surgery in the high-oxygen group.

It is very troubling that the protocol omitted so many crucial details regarding the usual standard of care for the individualized adjustment of FiO_2 and decisions about intubation, extubation, and mechanical ventilation in critically ill premature infants at the NRN medical centers; the risks associated with the experimental oxygen interventions; and the safety monitoring plan, all of which were essential for understanding the nature of the research and its risks. Lacking this information, it is unclear how the IRBs that reviewed the study were able to make the determinations required for IRB approval under the HHS human subjects protection regulations, particularly the determination that the risks to subjects were minimized.

III. General response to criticisms by the SUPPORT study investigators and others who have objected to OHRP's determinations of consent-form deficiencies

In response to OHRP's March 7 letter to UAB, the SUPPORT study investigators and others have issued numerous public statements in an attempt to defend the conduct of this study and the adequacy of the informed consent process. We therefore want to take this opportunity to explain some of the important, serious flaws in the arguments being made publicly by the investigators[31,32] and their supporters.[33,34]

The primary argument offered by those objecting to OHRP's finding of inadequate disclosure of study risks essentially goes as follows: The usual care for all critically ill, extremely premature infants in major academic NICUs across the U.S. at the time the study was conducted involved targeting their oxygen saturation *anywhere* between 85% and 95% without regard to *any* individual-specific clinical factors. For *all* such premature babies at *any time* during their NICU

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[30] *Ibid.*

[31] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med.* Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.

[32] Finer NN, Bell EF, Van Meurs K. Consent forms in a clinical trial for premature babies (letter to the editor). *The New York Times.* April 19, 2013. http://www.nytimes.com/2013/04/19/opinion/consent-forms-in-a-clinical-trial-of-premature-babies.html?ref=todayspaper. Accessed April 24, 2013.

[33] Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med.* Published online April 17, 2013. DOI: 10.1056/NEJMe1304996.

[34] Magnus D, Caplan AL. Risk, Consent, and SUPPORT. *N Engl J Med.* Published online April 18, 2013. DOI: 10.1056/NEJMp1305086.

stay, adjusting oxygen therapy to achieve *any* more narrowly defined target oxygen saturation band within the broader 85-95% range represented usual standard of care. Therefore, the experiment presented no risk to the babies.

This argument does not survive serious scrutiny. First, as noted above, the investigators themselves stated in the protocol that the higher oxygen saturation target range was the "more conventional" of the two oxygen saturation target ranges that were to be tested.

Second, taken to its logical conclusion, this argument would allow one to posit that the SUPPORT study's oxygen experiment could have been conducted with even more narrowly defined oxygen saturation target bands at the extremes of the 85% to 95% "normal range" without exposing premature babies to increased risks in comparison to usual standard of care in 2005. Experimental interventions limiting the target oxygen saturation ranges to increasingly narrower bands at opposite ends of the 85% to 95% range, combined with intentionally providing the medical team with inaccurate information about the babies' oxygen saturation levels, would have had an even more profound adverse impact on the morbidity and mortality risks for premature babies.

Third and most important, despite the gaps in scientific knowledge regarding oxygen management in premature infants at the time the SUPPORT study was initiated, it is inconceivable that in 2005, highly trained, expert neonatologists providing routine individualized care outside the research context did not adjust FiO_2 levels to achieve different oxygen saturation levels — in different babies and at different times for the same baby — within the broad range of 85-95% based on important clinical indicators of tissue oxygenation. These indicators would include base deficit levels (an elevated base deficit generally would be indicative of inadequate oxygen delivery to tissues of the body, and increasing the FiO_2 in order to increase the baby's oxygen saturation level would be one major treatment change to address this problem), other individual clinical factors, and consultations with parents regarding balancing of specific risks.

Thus, condensed and incomplete descriptions of the complex usual standard of care for managing supplemental oxygen treatments in extremely premature babies — such as the informed consent statements that "All of these saturations [i.e., 85-89% and 91-95%] are considered normal ranges for premature infants"[35] — were misleading to parents who gave consent for their babies to be in the SUPPORT study and, when repeated today, mislead the public.

To accomplish the goals of their oxygen experiment, the investigators first allowed a computer to randomly assign extremely premature babies to one of two narrowly constrained target oxygen saturation ranges, rather than individually adjusting oxygen based solely on the expert judgment of highly trained neonatologists. The investigators then provided the entire medical team caring for these babies with pulse oximeters that were intentionally programmed to provide inaccurate information regarding the oxygen saturation levels. Thus, because of these two protocol-specified procedures, babies in the study received experimental oxygen management

[35] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed May 7, 2013..

interventions that were substantially different from the usual standard of care they would have otherwise received had their parents not consented to the research.

IV. Responses to specific statements by the SUPPORT study investigators and others who have objected to OHRP's determinations of consent-form deficiencies

Beyond this flawed primary argument, Public Citizen addresses below some of the other public statements recently made by the SUPPORT study investigators,[36] the editors of *The New England Journal of Medicine* (*NEJM*),[37] and two bioethicists who authored a *NEJM* perspective article,[38] all of which attempt to defend the conduct of the SUPPORT study, especially the adequacy of the informed consent process.

A. SUPPORT study investigators

The following are some recent statements made by the SUPPORT study investigators, with our comments in response in italics after each:

> Investigators: Death was included in the primary outcome because it competes with retinopathy, not because a difference in mortality was expected.[39]
>
> *Our comments: The investigators argue that they did not expect to see an increased rate of death in the low-oxygen group, and therefore it was not a risk that needed to be disclosed in the consent forms signed by parents of babies enrolled in the study. However, this argument is belied by multiple other statements made by the investigators in the protocol and elsewhere.*
>
> *First, the purpose of the SUPPORT study was to test different experimental strategies for managing oxygen and ventilation therapy in premature infants and assess their effects on primary composite endpoints that all included death as an outcome. This is reflected in the study's primary hypotheses and in the protocol's statistical analysis plan.[40] Death obviously was the most important component for these primary endpoints. Death alone also was pre-specified as an important secondary endpoint across all four study groups. Comparisons of the primary and secondary outcomes across all four study groups was planned and performed with two-sided P-values.[41,42] The plan to use two-tailed P-values*

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[36] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med.* Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.
[37] Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med.* Published online April 17, 2013. DOI: 10.1056/NEJMe1304996.
[38] Magnus D, Caplan AL. Risk, Consent, and SUPPORT. *N Engl J Med.* Published online April 18, 2013. DOI: 10.1056/NEJMp1305086.
[39] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med.* Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.
[40] NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 **(revised September 16, 2004; updated March 28, 2005).** http://www.nih.gov/icd/od/foia/library/Protocol.pdf. Accessed April 24, 2013.
[41] *Ibid.*
[42] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.

when analyzing the data for the primary and secondary endpoints is an acknowledgement that the investigators wanted to test for two plausible possibilities. Thus, for the comparison between the low- and high-oxygen groups, the investigators clearly planned to assess whether the composite efficacy endpoint of death plus retinopathy, as well as the secondary endpoint of death alone, would have been higher or lower in one group versus the other.

Second and more important, by correctly stating that "[death] competes with retinopathy,*"*[43] *the investigators acknowledged that they also were aware — prior to the initiation of the study — that trying to decrease the risk of retinopathy could potentially increase the risk of death. The fact that the investigators may not have expected that there would be a difference in mortality between the two experimental groups is not a valid basis for concluding that death was not a risk of the experiment.*

There should have been a concern among both the investigators and the IRBs at the time the research protocol was developed and reviewed that mortality could be increased in the low-oxygen group. An increase in retinopathy also should have been recognized as a risk for the high-oxygen group. Moreover, because the study lacked randomization of babies to a routine standard-of-care control group, we are left not knowing how the two experimental treatments compared to usual standard of care at the time.

Clearly, the parents should have been told that: (a) one primary purpose of the experiment was to determine which range of oxygen level would have a higher rate of death, and (b) death was a risk of the research depending on the randomized group assignment of each baby. The failure to disclose this information represented a serious violation of research ethics.

Investigators: The best evidence available when we planned the study was that oxygen saturations of 70 to 90% were associated with less retinopathy without an increase in mortality.[44]

Our comments: To support this statement, the investigators cite a small, non-randomized, uncontrolled, retrospective, observational study of premature babies born in northern England between 1990 and 1994 as their "best evidence" for believing that oxygen saturation targets could be as low as 70% without increasing mortality.[45] *The study compared survival rates and incidence of retinopathy of prematurity in four cohorts of premature babies who had been cared for in neonatal intensive care units that used different target saturation ranges (88-98%, 85-95%, 84-94%, and 70-90%). The authors of the cited study themselves noted that "***Staff always aimed to maintain saturation in the top half of the target range (particularly when the lower limit of this range was less than 85%)***" [emphasis added]. The study also provided incomplete data on baseline clinical parameters that could have affected prognosis for babies in each cohort. Most*

[43] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med.* Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.
[44] *Ibid.*
[45] Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 2001;84:F106-F110.

importantly, the study provided no data on the actual oxygen saturation levels achieved for babies in each cohort. As a result, no useful or valid conclusions can be drawn from this study about oxygen management in extremely premature infants, and the data certainly were insufficient to provide any reasonable assurance that the lower oxygen saturation target in the SUPPORT study would be "without an increase in mortality [risk]". Indeed, as discussed above, that was one of the primary questions to be answered by the SUPPORT study's oxygen experiment.

Investigators: Families were clearly informed that retinopathy was a known risk to their babies and that the SUPPORT study was conceived to test oxygen targets at the lower end of the recommended range to reduce the risk of retinopathy.[46]

Our comments: Families eventually may have been informed in the context of the babies' clinical care post-delivery about retinopathy being a well-known complication of extreme prematurity, but a detailed discussion of this issue was unlikely to have occurred in the midst of premature labor, when informed consent was to have been sought. Twenty of the 22 IRB-approved consent forms for the oxygen experiment certainly failed to disclose that assignment to the high-oxygen group could have increased the risk of retinopathy. This is in striking contrast to the benefits section of the majority of the consent forms, which did tell parents that the low-oxygen experimental group had the possible benefit of lowering the risk of retinopathy. To present only a description of the potential benefits of lowering the risk of retinopathy if the baby was assigned to the low-oxygen group without disclosing any risks of the experiment again was misleading to the parents of the enrolled babies.

Investigators: The infants in both treatment groups had lower rates of death before discharge (16.2% in the higher-oxygen-saturation group and 19.9% in the lower-oxygen-saturation group) than did those who were not enrolled (24.1%) and historical controls (23.1%), and rates of blindness did not differ between the treatment groups.[47]

Our comments: It is not clear why the investigators think these data are important or relevant since they claimed — incorrectly, as discussed above — that all babies enrolled in the study received the same care as babies not in the study (i.e., the usual standard of care). Regardless, such post hoc comparisons to a contemporaneous group of babies not enrolled in a prospective, randomized clinical trial or to a historical comparison group are subject to bias and confounding factors and are incompatible with making definitive scientific conclusions. If the investigators thought that such a standard-of-care control group was necessary, it should have been incorporated into the design of their randomized controlled study.

Furthermore, the investigators' comparison of the mortality rates seen in the SUPPORT study babies to the mortality rate of 24.1% for a non-enrolled patient group appears to be derived from the research paper published by the SUPPORT study investigators in

[46] Carlo WA, Bell EF, Walsh MC. Oxygen saturation targets in extremely premature infants (letter to the editor). *N Engl J Med.* Published online on April 17, 2013. DOI: 10.1056/NEJMc1304827.
[47] *Ibid.*

the March 2012 issue of the journal Pediatrics, *entitled "Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative."*[48] *The paper compared key baseline demographic and clinical factors for the 1,316 premature babies enrolled in the SUPPORT study (enrolled babies) to those of 3,054 premature babies at the SUPPORT study hospitals who were eligible for the study but did not enroll (non-enrolled babies). Important data from the* Pediatrics *paper demonstrates that the non-enrolled babies overall were sicker and, at the start, more at risk of death than babies in the SUPPORT study. Thus, the data from this paper do not support the conclusion that enrollment in the study resulted in better survival.*

Finally and most important, such post hoc comparisons are ultimately irrelevant with respect to assessing the risks of the experiment and the adequacy of the consent form and process at the time the study was submitted to the IRBs for initial review.

B. Editorial in *The New England Journal of Medicine (NEJM)*

The following are some statements made in a recent *NEJM* editorial attempting to defend the unethical conduct of this study and criticizing the actions taken by OHRP in this case, with our comments in response:

NEJM: So it is easy to imagine the stress when, in 2005, your new baby decides to come into the world after only 6 months of gestation, long before your pregnancy has reached term. You know that extremely premature babies like yours may not survive, but you are reassured that you are giving birth at an academic medical center with a sophisticated nursery for premature newborns and with physicians who have extensive experience with very preterm infants.[49]

Our comments: The editorial correctly calls attention to the circumstances under which consent was sought from the parents of babies enrolled in the SUPPORT study. Mothers (and fathers, if present) were approached about enrolling in the study just prior to the months-too-early delivery of their babies that placed the parents under significant psychological and emotional stress. Moreover, many of these parents were likely very young and educationally or economically disadvantaged. Any of these factors alone or in combination made the parents highly vulnerable to coercion or undue influence. They were likely to be very trusting of the doctors caring for them. Many, if not most, were ill-prepared to understand the complexities of usual standard of care for premature babies, let alone the complexities of the experimental interventions, even if the investigators had provided a complete disclosure of the purpose, nature, and risks of the research.

A review of the SUPPORT study protocol reveals no discussion of the additional protections that were to have been put in place to ensure that these highly vulnerable parents were protected from undue influence or coercion. For example, independent

[48] Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics.* March 2012;129(3):480-484.
[49] Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT (editorial). *N Engl J Med.* Published online April 17, 2013. DOI: 10.1056/NEJMe1304996.

monitors of the consent process would have been an appropriate procedure. It would be important to know whether any IRB that reviewed and approved this study required implementation of such additional protections.

NEJM editorial: Without research studies your neonatologist would simply be guessing about what is best rather than knowing what is best for your child…

For a baby not enrolled in any of these trials, the specific range of oxygen saturation targeted within these broader guidelines was left to the discretion of the child's physician, who lacked data to guide decision making.[50]

Our comments: It is misleading to suggest that neonatologists at the time the SUPPORT study was conducted were simply guessing when making individualized treatment decisions about oxygen management for their patients. Although imperfect, there were substantial data in the medical literature to guide oxygen therapy in premature babies. These data were supplemented to varying degrees by extensive clinical experience. In addition, this statement suggests a belief, also apparently held by the investigators, that there exists some yet-to-be-determined universal "sweet-spot" oxygen saturation level for all premature babies, the details of which could be found from such an experiment. It is implausible that such a universal sweet spot exists.

NEJM editorial: This response is disappointing, because it does not take into account either the extent of clinical equipoise at the time the study was initiated and conducted or that the consent form, when viewed in its entirety, addressed the prevalent knowledge fairly and reasonably.[51]

Our comments: First, whether clinical equipoise between the two oxygen study groups existed at the time the SUPPORT study was conducted is completely irrelevant to whether the consent form and process were adequate. Second, the existence of clinical equipoise between study groups within a randomized clinical trial does not mean that the study is without risk. Third, for many babies in the study, clinical equipoise likely did not exist between the low- and high-oxygen experimental groups. Finally, as discussed in earlier sections of this report, the descriptions of the study's experimental procedures in the consent form were incomplete and misleading.

C. *NEJM* perspective article

Finally, the following are some statements made in a recent *NEJM* perspective piece attempting to defend the unethical conduct of the SUPPORT study and criticizing the actions taken by OHRP in this case, with our comments in response:

NEJM perspective article: A great deal of effort is under way to make it easier and less expensive to conduct prospective, randomized comparative effectiveness research. Some of the options for conducting such research take advantage of the fact that there is no

[50] *Ibid.*
[51] *Ibid.*

additional risk to being randomly assigned to one or another equally well-supported treatment option that falls within the standard range of care in clinical practice… The OHRP reprimand is troubling both because it has sown confusion and focused unwarranted negative attention on valuable research and because it incorrectly suggests that the risk of comparative effectiveness research involving infants, or any other group, is equivalent to the risk of research involving randomization to a novel intervention…

The SUPPORT investigators believed that since all the study infants would receive oxygen levels within the prevailing standard of care, there was no additional risk to being enrolled in the trial. Indeed, it has been argued that the research should have been eligible for a waiver of documentation of informed consent, since there was no basis for claiming an increase in risk from enrolling in the trial versus receiving standard clinical care.[52]

Our comments: These statements demonstrate a lack of understanding of how the SUPPORT study was conducted, the difference between the complex experimental procedures used in the study to manage and monitor oxygen levels in the subjects and usual standard of care for premature infants, and the risks posed by these experimental procedures, as discussed in detail above in prior sections of this report.

Labeling the SUPPORT study as "comparative effectiveness research" is a gross mischaracterization because the two experimental oxygen interventions were clearly novel and not consistent with the usual standard of care. Furthermore, even if this characterization were accurate, the presumption that all randomized "comparative effectiveness research" studies pose no risk to subjects is nonsensical.

Attempts to discount the risks posed by the SUPPORT study's oxygen experiment by using the benign-sounding label "comparative effectiveness research" only serve to confuse the public. Other much more appropriate terms that could be used to describe the SUPPORT study and more accurately convey its nature are "comparative safety research" or "comparative harmfulness research." However, the use of such terms would have drawn even more attention to the absence of risk information regarding the oxygen experiment part of the study in the consent forms.

NEJM perspective article: Among neonatologists, the standard of care varied — too much oxygen was associated with retinopathy of prematurity and possible blindness, but too little oxygen risked neurologic damage and death.[53]

Our comments: This statement accurately portrays the tradeoff in risk of retinopathy from exposure to too much oxygen and the risk of brain injury and death from too little oxygen, a tradeoff that the SUPPORT study investigators, but not the parents, also must have been aware of.

[52] Magnus D, Caplan AL. Risk, Consent, and SUPPORT. *N Engl J Med.* Published online April 18, 2013. DOI: 10.1056/NEJMp1305086.
[53] *Ibid.*

NEJM perspective article: Given that there was variation in clinical practice at the time the study was mounted, it is not clear how randomization among treatment options could have created novel risk over random physician preference.[54]

Our comments: Variation in clinical practice does not mean that physician preferences are random. Furthermore, given the information presented in prior sections of this report, it is misleading to suggest that neonatologists at the time the SUPPORT study was conducted were simply guessing and randomly choosing oxygen saturation targets when making decisions about oxygen management. More important, the investigators themselves stated in the SUPPORT protocol that the higher oxygen range was the "more conventional" target range for managing oxygen therapy in premature infants. Finally, as also discussed in detail in section II of this report, the research procedures involved more than just randomization to one of two experimental oxygen saturation target groups. The experiment also involved provision of intentionally inaccurate oximetry information to the medical teams caring for the premature babies enrolled in the SUPPORT study. This experimental intervention cannot reasonably be construed as standard clinical practice.

NEJM perspective article: With regard to SUPPORT, the OHRP is asking that research be described as riskier than it really is and is suggesting that the parents were duped into enrolling their frail infants in dangerous research.[55]

Our comments: As previously discussed in detail in prior sections of this report, the oxygen experiment component of the SUPPORT study posed significant, life-threatening risks to the frail babies enrolled in the study. The failures to disclose critically important information regarding the purpose, nature, and risks of the research to parents of the SUPPORT study babies represented a serious violation of research ethics.

V. Conclusions

The new information discussed in this report affirms the appropriateness of OHRP's determination in its March 7, 2013, letter to UAB that the UAB IRB-approved consent form failed to mention the serious, reasonably foreseeable risks related to the part of the study comparing two experimental strategies for managing oxygen in extremely premature infants. Those risks, correctly identified by OHRP, included increased risks of brain injury; retinopathy of prematurity, which can lead to blindness in severe cases; and death, depending on the randomized group assignment of each baby. Indeed, the UAB IRB-approved consent form misled parents of prospective subjects by essentially indicating that the oxygen experiment component of the SUPPORT study presented no risk.

Moreover, the new information demonstrates that the deficiencies of the UAB IRB-approved consent form were far more significant than those discussed in OHRP's March 7 letter. The agency should have cited UAB and all other participating institutions for additional serious deficiencies in the IRB-approved consent form regarding the lack of disclosure of critically

[54] *Ibid.*
[55] *Ibid.*

important information about the protocol-specified purpose and nature of the oxygen experiment. In particular, the IRB-approved consent forms in many, if not all, cases either did not disclose at all or did not accurately describe the following:

(1) The experimental procedure of using pulse oximeters that were intentionally miscalibrated to provide the medical teams caring for the premature babies in the study with oxygen saturation readings that were either inaccurately low or inaccurately high. (Only 11 consent forms disclosed this procedure in some way, but none explained how this experimental procedure could have impacted important clinical decisions related to the babies' care.)

(2) The substantial, reasonably foreseeable risks of harm from intentionally providing the medical teams caring for the babies in the study with inaccurate information regarding the babies' oxygen saturation levels. This experimental procedure may have adversely impacted important clinical decisions regarding whether to intubate a baby and start mechanical ventilation or whether to extubate an intubated baby and discontinue mechanical ventilation. For example, because of this experimental procedure:

   (a) Some babies in the high-oxygen group may have undergone protocol-driven intubations and been placed on mechanical ventilation when such procedures were not clinically indicated. This could have unnecessarily exposed some babies to increased risk of: (i) trauma to the mouth and gums during intubation; (ii) trauma to the trachea, resulting in bleeding and puncture of the airway during intubation; (iii) pneumothorax (collapsed lungs, possibly resulting in the need for insertion of chest tubes); (iv) pneumonia during mechanical ventilation; and (v) death.

   (b) Some babies in the low-oxygen group may have had actual clinical indications for intubation and mechanical ventilation, but because of inaccurate oxygen saturation levels, these treatments may have been inappropriately delayed. This could have unnecessarily exposed some babies in the low-oxygen group to increased risk of prolonged hypoxemia with inadequate oxygen delivery to the brain, resulting in neurological damage and possibly death.

(3) The investigators' characterization in the protocol, but not in the consent form, of the high-oxygen target levels as being "more conventional" and, by implication, the low-oxygen target levels being less conventional. (Only two consent forms suggested an oxygen saturation range that was most commonly used in routine practice.)

(4) An explanation of how the experimental procedures for managing the oxygen therapy of the babies deviated from the usual standard of care the babies would have received had they not been enrolled in the study.

A particularly disturbing finding in Public Citizen's analysis of the complete protocol and the IRB-approved consent forms is that most consent forms included an extraordinarily misleading statement, such as the following:[56]

[56] IRB-approved consent form for the SUPPORT trial. http://www.citizen.org/documents/support-study-consent-form.pdf. Accessed May 7, 2013.

"There is no known risk to your baby from monitoring with the pulse oximeters used for this study."

or

"Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant."

The absence of critical elements of information about the purpose, nature, and risks of the complex SUPPORT study's oxygen experiment, combined with the inclusion of statements indicating that the experimental procedures had no known risks, denied the parents of babies enrolled in the trial the opportunity to make an informed decision when they gave consent for the research. The failure to disclose this critically important information to the parents represented a serious violation of research ethics.

Finally, a review of the complete protocol appears to indicate that the IRBs that approved the study lacked crucial information that would have been necessary for them to determine whether risks to the babies enrolled in the research were minimized by using procedures consistent with sound research design and that did not unnecessarily expose subjects to risk. Important details regarding each of the following were omitted from the protocol:

(1) a description of the usual standard of care for critically ill premature babies regarding such critical issues as the individualized adjustment of FiO_2 and decisions about intubation, extubation, and mechanical ventilation at the NRN medical centers;

(2) the risks associated with the experimental oxygen interventions, including those related to use of intentionally miscalibrated pulse oximeters;

(3) the plan for unblinding the NICU medical teams when the masking procedure using intentionally miscalibrated pulse oximeters posed a threat to the health of the babies; and

(4) the safety monitoring plan.

The omitted information was essential for understanding the nature of the research and its risks. Lacking this information, it is unclear how the IRBs that reviewed the study were able to make the determinations required for IRB approval under the HHS human subjects protection regulations, particularly the determination that the risks to subjects were minimized.

Some critics of OHRP's determinations regarding the SUPPORT study argue that the agency's action in this case poses a threat to biomedical research and the advancement of medical knowledge and innovation. However, the real threat to such scientific endeavors is unethical research, which understandably undermines the public's trust in the motives and conduct of researchers. Conformance with the fundamental ethical principles for conducting human subjects research must never be sacrificed in the quest to advance medical knowledge. Such conformance is necessary to preserve the public's trust in the motives and conduct of researchers.

Appendix

Public Citizen Reviewed IRB-Approved SUPPORT Study Consent Forms for the Following Institutions:

- Cincinnati Children's Hospital
- Duke University Health System
- Emory University School of Medicine/Grady Memorial Hospital and Crawford W. Long Hospital
- Indiana University-Purdue University of Indiana and Clarian
- Intermoutain Medical Center and Primary Children's Medical Center
- Sharp Mary Birch Hospital for Women
- Stanford University
- Tufts Medical Center
- University Hospitals Case Medical Center, Cleveland, OH
- University of Alabama at Birmingham
- University of California, San Diego
- University of Iowa
- University of Miami/Jackson Memorial Hospital (Approved by the Western IRB in Olympia, WA)
- University of New Mexico Health Sciences Center
- University of Rochester Medical Center
- University of Texas Health Science Center and Memorial Hermann Children's Hospital
- University of Texas Southwestern Medical Center at Dallas/Parkland Health & Hospital System and Children's Medical Center
- University of Utah
- Wake Forest University School of Medicine, Forsyth Medical Center
- Wayne State University/Hutzel Women's Hospital
- Women and Infant's Hospital of Rhode Island
- Yale University School of Medicine/Yale-New Haven Hospital

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Stile, Christina (NIH/NICHD) [E]
Subject: RE: photo of baby?
Date: Thursday, May 23, 2013 9:51:00 AM
Attachments: image004.png

Great
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 9:51 AM
To: Stile, Christina (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: photo of baby?

I'll go ahead and send if I can cut and paste the picture – and copy you all so if she has questions you can answer directly

Mona

Mona Jaffe Rowe, M.C.P.
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Email: rowem@mail.nih.gov

From: Stile, Christina (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 9:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: photo of baby?

ok. i believe the others we have are also slightly "older" so they wouldn't work either.

mona, should i send to kathy?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 9:00 AM
To: Stile, Christina (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: photo of baby?

The one with the blue hat is the best for the SUPPORT study; the second and third babies would likely not have qualified as they appear to be more mature that the population studied in the trial.

Rose

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Stile, Christina (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 8:59 AM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Stile, Christina (NIH/NICHD) [E]
Subject: RE: photo of baby?

here are some—i'm working on getting the others

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 8:23 AM
To: Stile, Christina (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: photo of baby?

Hi Christina –we have three pictures of preemies that we used in the snapshot book - --we purchased those I believe -- --do we need to get extra permission if they are to be used in another publication or a published journal

We will need these first thing this AM – I am in a meetings off and on in the AM- could you get those together and send the pictures to Rose and me to look at - -I will take my new ipad – hopefully it will be easier to see the pictures – would it be possible to cut and paste it into the email? Thanks!

Mona

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 23, 2013 6:21 AM
To: Rowe, Mona (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: Re: photo of baby?

Please use a file one - I may not have primary source permission for the ones I have
Thanks
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 10:32 PM
To: Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: photo of baby?

We probably have many in our files – let me check with our web content folks – unless Rose has some readily on hand

---

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 22, 2013 9:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: photo of baby?

We are looking for a photo of preemie that could accompany nejm article (draft attached).
Got any pics of tiny babies that we could use?

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

No virus found in this message.
Checked by AVG - www.avg.com
Version: 2013.0.2904 / Virus Database: 3162/6338 - Release Date: 05/19/13

No virus found in this message.
Checked by AVG - www.avg.com
Version: 2013.0.2904 / Virus Database: 3162/6338 - Release Date: 05/19/13

Blansfield, Earl (NIH/NICHD) [E]

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, May 23, 2013 8:09 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: softer, gentler, shorter nejm draft
Attachments: NEJM draft - support statement 5-22-13 - ag fc.docx

And here are my edits on top of Alan's. I think the (b)(5)

I'm happy to transmit this to (b)(5) once the references are finalized and other clean up occurs. Just let me know.

FC

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 10:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: softer, gentler, shorter nejm draft

My thoughts attached.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
31 Center Drive
Building 31, Room 2A03
Bethesda, MD 20892-2425

Phone: 301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 22, 2013 7:56 PM
To: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: softer, gentler, shorter nejm draft

If you guys get comments back tonight, I can incorporate and send to hhs

Page 1346 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1348 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 8:15 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Funding for NRN and SUPPORT

Hi Kathy -- Rose asked me to get back with you re: our estimates for the Neonatal Research Network and the SUPPORT trial. We did some estimates and confirmed with our budget officer. The summary numbers and worksheet are below.

- Bewteen FY 2004 and FY 2012 - NRN funding ranged from $8.9 million to $11.9 million -- depending on the year (we changed the model for capitation during this time, etc.)
- The average funding for the NRN was $9.9 million
- We estimate, based on the assumption that the SUPPORT network was about 1/6 of the total NRN expenditures plus NHLBBI co-funding, that the total cost of the SUPPORT trial for all four 4 years (original study and analysis) was about $11.5 million. This averaged to $2.875 million per year.

Hope this helps. Let us knowif you have questions. Mona

Copy of NRN Support Trial Inv...

Mona

Mona Jaffe Rowe, M.C.P.
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NICHD NEONATAL RESEARCH NETWORK SUPPORT TRIAL TOTAL INVESTMENT (FYS2004-2007 FY 2012)

Neonatal Research Networl

Fiscal Years	FY 2004	FY 2005	FY 2006	FY2007
NRN Sites	$7,762,866	$6,249,962	$6,027,215	$5,960,764
DCC	$2,874,693	$2,926,692	$2,948,906	$3,014,224
Total NRN	$10,637,559	$9,176,654	$8,976,121	$8,974,989
Support Trial				
Total NRN	$10,637,559	$9,176,654	$8,976,121	$8,974,989
% SUPPORT (.166)	0.1660	0.1660	0.1660	0.1660
Subtotal SUPPORT Trial (NICHD)	$1,765,835	$1,523,325	$1,490,036	$1,489,848
NHLBI Co-funding	$1,300,000	$1,300,000	$1,300,000	$1,300,000
[redacted]				

4-05351

NICHD NEONATAL RESEARCH NETWORK SUPPORT TRIAL TOTAL INVESTMENT (FYS2004-2007 FY 2012)

‹ and SUPPORT Trial: Estimated Funding

FY2008	FY2009	FY2010	FY2011	FY 2012
$6,505,880	$3,326,831	$4,041,092	$5,456,238	$5,577,976
$3,007,766	$6,092,680	$5,681,639	$5,312,036	$6,308,777
$9,513,646	$9,419,511	$9,722,731	$10,768,274	$11,886,753
				AVG. FY 04 -12
$9,513,646	$9,419,511	$9,722,731	$10,768,274	$11,886,753
0.0000	0.0000	0.0000	0.0000	0.0000
$0	$0	$0	$0	$0

NICHD NEONATAL RESEARCH NETWORK SUPPORT TRIAL TOTAL INVESTMENT (FY S2004-2007 FY 2012)

Totals
$50,908,824
$38,167,413
[redacted]
$9,897,360
$89,076,238
0.0000
[redacted]
$5,200,000
$11,469,044

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Nejm!!! Woo hoo!!
Date: Wednesday, May 22, 2013 4:12:02 PM

---

wow

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 6:26 AM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: Nejm!!! Woo hoo!!

FYI
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 06:18 AM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Nejm!!! Woo hoo!!

The total costs per year for the NRN are hard to gauge depending on actual recruitment. I can work with Mona to get some numbers- do you want FY13 or costs during the time the SUPPORT study was conducted?

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 10:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Nejm!!! Woo hoo!!

Yes! I raised this with (b)(but she is not... Well...

Do we know how much we spent on support and spend on nrn? Number could be useful.

Cc-ing rose who is always a peach.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH

301 496 1455
kathy.hudson@nih.gov

On May 21, 2013, at 10:05 PM, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov> wrote:

> I like that strategy but bow to you who know (b)(5)
(b)(5) I would add, but only IF effective, that (b)(5)
(b)(5)
>
> A.
>
> Alan E. Guttmacher, M.D.
> Director
> Eunice Kennedy Shriver National Institute of Child Health and Human Development
> National institutes of Health
>
> On May 21, 2013, at 9:15 PM, "Devaney, Stephanie (NIH/OD) [E]" <stephanie.devaney@nih.gov> wrote:
>
>> This is wonderful news! Should I take a stab at cutting it down and making the other changes he suggested?
>>
>>
>> ----- Original Message -----
>> From: Hudson, Kathy (NIH/OD) [E]
>> Sent: Tuesday, May 21, 2013 07:40 PM
>> To: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
>> Subject: Nejm!!! Woo hoo!!
>>
>> Just got off the phone with drazen. Jeff wants the article. He will publish on line next Wednesday. Woo hoo! Go team!!!
>>
>> He wants it more in "our voice," needs it at 1200 words, wants us to refer to other published stuff rather than retelling the tale (word savings there), and wants a picture (baby?).
>>
>> Okay. Now for strategy.
>>
(b)(5)
started.
>>
>> I said we were aiming for nejm article. (b)(5)
(b)(5)
>>
(b)(5)
>>
>> I think (b)(5)
>>
>> But we (b)(5)
>>

>> Thoughts?
>>
>>
>>
>>
>>
>>
>>
>> Kathy Hudson, Ph.D.
>> Deputy Director for Science, Outreach, and Policy
>> NIH
>> 301 496 1455
>> kathy.hudson@nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Nejm!!! Woo hoo!!
Date: Wednesday, May 22, 2013 4:02:00 PM

Mona

This looks fine to me – do you want me to send to Kathy or will you?

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 3:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Nejm!!! Woo hoo!!

Mona

Mona Jaffe Rowe, M.C.P.

Associate Director for Science Policy,

Analysis and Communication

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Phone: 301.496.1877/Fax: 301.496.0588

Email: rowem@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 3:51 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: Nejm!!! Woo hoo!!

Kathy -- Rose asked me to get back with you on our estimates for the Neonatal Research Network. We computed and checked with our budget officer. So here are some summary numbers for you. The worksheet is attached below.

- The NRN funding ranged from $8.9 million to $11.9 million -- depending on the year (we changed the model for capitation during this time, etc.)
- The average funding for the NRN was $9.9 million
- We estimate, based on the assumption that the SUPPORT network was about 1/6 of the total NRN expenditures, in addition to the bolus of funds from the NHLBI, that the total cost of the SUPPORT trial for all four 4 years (original study and analysis) was $11.5 million. This averaged to $2.875 million per year.

Hope this helps. Mona

<< File: Copy of NRN Support Trial Investment Chart 5-22-2013 final.xlsx >>

Mona

Mona Jaffe Rowe, M.C.P.

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Email: rowem@mail.nih.gov

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 6:42 AM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: Fw: Nejm!!! Woo hoo!!

Mona-

Can we discuss this morning? I will be in at 815

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----

From: Higgins, Rosemary (NIH/NICHD) [E]

Sent: Wednesday, May 22, 2013 06:18 AM

To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]

Cc: Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]

Subject: RE: Nejm!!! Woo hoo!!

The total costs per year for the NRN are hard to gauge depending on actual recruitment. I can work with Mona to get some numbers- do you want FY13 or costs during the time the SUPPORT study was conducted?

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch CDBPM, NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]

Sent: Tuesday, May 21, 2013 10:09 PM

To: Guttmacher, Alan (NIH/NICHD) [E]

Cc: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]

Subject: Re: Nejm!!! Woo hoo!!

Yes! I raised this with Caya but she is not... Well...

Do we know how much we spent on support and spend on nrn? Number could be useful.

Cc-ing rose who is always a peach.

Kathy Hudson, Ph.D.

Deputy Director for Science, Outreach, and Policy NIH

301 496 1455

kathy.hudson@nih.gov

On May 21, 2013, at 10:05 PM, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov> wrote:

> I like that strategy but bow to you who know Department leadership better as to what arguments will beast effective. I would add, but only IF effective, that as sponsors of the NRN, we have a special responsibility to salvage the reputations of dogged and highly ethical investigators whose careers have been needlessly and wantonly sullied. They deserve better than to have their ethics called in question by federal officials and, as a result, by such as the NYT.

>

> A.

>

> Alan E. Guttmacher, M.D.

> Director

> Eunice Kennedy Shriver National Institute of Child Health and Human

> Development National institutes of Health

>

> On May 21, 2013, at 9:15 PM, "Devaney, Stephanie (NIH/OD) [E]" <stephanie.devaney@nih.gov> wrote:

>

>> This is wonderful news! Should I take a stab at cutting it down and making the other changes he suggested?

>>

>>

>> ----- Original Message -----

>> From: Hudson, Kathy (NIH/OD) [E]

>> Sent: Tuesday, May 21, 2013 07:40 PM

>> To: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E];

>> Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]

>> Subject: Nejm!!! Woo hoo!!

>>

>> Just got off the phone with drazen. Jeff wants the article. He will publish on line next Wednesday. Woo hoo! Go team!!!

>>

>> He wants it more in "our voice," needs it at 1200 words, wants us to refer to other published stuff rather than retelling the tale (word savings there), and wants a picture (baby?).

>>

>> Okay. Now for strategy.

>>

(b)(5) called today and asked about our articles. (b)(5)

(b)(5)

>>

(b)(5)

>>

>> So, I think we have (b)(5)

(b)(5)

(b)(5) Plus, Jerry has been pitching his views to both jama and nejm!!! Jeff said he would readily publish Jerry's apology !

>>

>> Sorry for digression but of interest.

>>

>> I think (b)(5)

>>

>> But we (b)(5)

>>

>> Thoughts?

>>

>>

>>

>>

>>

>>

>>

>> Kathy Hudson, Ph.D.

>> Deputy Director for Science, Outreach, and Policy NIH

>> 301 496 1455

>> kathy.hudson@nih.gov

No virus found in this message.

Checked by AVG - www.avg.com

Version: 2013.0.2904 / Virus Database: 3162/6338 - Release Date: 05/19/13

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Plummer, Mary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: RE: Council Presentation: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trail)
Date: Wednesday, May 22, 2013 9:12:00 AM

This is fine (change Trail to Trial)

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Plummer, Mary (NIH/NICHD) [E]
Sent: Wednesday, May 22, 2013 9:11 AM
To: Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Council Presentation: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trail)

Do you have any issues with the tile change before I respond to Dr. Carlo.

Tite: The Surfactant Positive Airway Pressure and Pulse Oximetry Trail in Extremely Preterm Infants (SUPPORT Trail)

Mary

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, May 22, 2013 8:50 AM
To: Plummer, Mary (NIH/NICHD) [E]
Cc: Becky Brazeel; swilliams@peds.uab.edu; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Council Presentation: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trail)

Dear Ms. Plummer:

I look forward to the presentation. It would be best to modify the title from "...Extremely Low Birth Weight..." to "...Extremely Preterm...".

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Plummer, Mary (NIH/NICHD) [E] [mailto:plummerm@exchange.nih.gov]
Sent: Tuesday, May 21, 2013 10:39 AM
To: Wally Carlo, M.D.
Cc: Becky Brazeel; swilliams@peds.uab.edu; Maddox, Yvonne (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Council Presentation: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trail)

Dear Dr. Carlo:

On behalf of Drs. Alan Guttmacher, Director and Yvonne Maddox, Deputy Director, NICHD, I am pleased that you have agreed to speak at the June 6, 2013, meeting of the National Advisory Child Health and Human Development Council. The Council meeting will convene at 8:00 a.m., Building 31, C-Wing, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland. Attached is a copy of the Council membership roster and DRAFT Tentative Agenda.

Your presentation entitled *The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trail)* should be no longer than 20 minutes in duration which will include the questions and answers session. It is expected that the overall presentation will begin at 11:00 a.m. and conclude at 12:00 p.m. **It would be appreciated if you could bring with you to the Council meeting a one-page, typewritten summary of your presentation**. This summary will be used for inclusion in the Minutes of the Meeting which must be prepared immediately following Council adjournment.

Information Technology Guidelines

The meeting room is equipped with DVD capabilities and a podium laptop. Please let me know if you have any additional audio-visual requirements. If you have a PowerPoint presentation you will need to e-mail your slide presentation to Bonnie Snell, Information Technology Consultant, Booz Allen Hamilton at: snell_bonnie@bah.com or snellbe@mail.nih.gov no later than Tuesday, **June 4**. Also, please advise if you will be using videos or advanced animations in your presentation.

Council meetings are broadcast for the NIH staff and the general public using the NIH Videocast System. In addition, a member of the Council will be participating in the meeting remotely using Adobe Connect. Your presentation will also be posted to the Institute's Public and Council Member web sites for review prior to the Council meeting. It is vital that we receive your final PowerPoint

presentation by the due date (June 4) in order to be posted on the Council member web site and tested with the Videocast and Adobe Connect technology. If the due date causes you a hardship, please let us know and we will work with you to accommodate your needs.

Travel Information

Please arrange your travel through the NIH Travel Management Center, Omega World Travel. You can contact Omega Toll Free at: 1-800-253-1098 (York, Pennsylvania) at *regular scheduled office hours* of 8:00 a.m. to 5:30 p.m. EST. Additional Omega contact information is as follows: 1) *after hours emergency number* is 1-800-285-6342; 2) FAX Number is 717-699-2131; and 3) e-mail contact is Lea Flickinger, NIH Councils Lead Agent and her e-mail address is Lflickinger@owt.net In an *After Hours* situation, you need to use the ID Code C-5GL-NIHCOUNCIL. Due to cost limitations, tickets will not be issued until two business days before your departure date. In support of the federal government's Efficient Spending Initiative, it will be necessary to use the airport that offers the lowest fare, that is, a contract fare.

Once your reservations have been processed by Omega, they will fax or e-mail your itineraries and send the tickets via UPS. **Please book your reservation by May 24, 2013 (Friday).** Once travel plans are made with Omega, they will e-mail us your itinerary and we will then process your travel order. When the travel authorization is processed, it will be e-mailed to you. If there are any last minute changes in your travel arrangements, please contact Omega. If you should have any questions, please contact Mr. Ron Livingston at (301) 435-6910 or (301) 594-7232.

Hotel Information

Sleeping room accommodations have been made at the Hyatt Regency Bethesda, Maryland, One Bethesda Metro Center (7400 Wisconsin Avenue, Bethesda, Maryland) for the night of Wednesday, June 5, 2013 at $224.00 per night plus 15% tax. The hotel is located on the Metro Red Line at the Bethesda Station stop which is positioned directly beneath the hotel. For more Metro information, visit www.wmata.com. **Please go to the following link for easy reservation access** https://resweb.passkey.com/go/NIC4. **The group code is NIC4 and the meeting will read as NICHD/Advisory Council.**

You must book your reservation by calling the hotel and providing them with a major credit card number with the expiration date. The hotel phone number is (301) 657-6418. You need to reserve your room by May 24, 2013 (Friday). If you will be arriving after 6:00 p.m., please inform the hotel so they do not resell the room. Please identify yourself as a member of the Child Health Advisory Council, and your meeting code is NIIC. The Hotel will release your reservation on **May 24, 2013 at 6:00 p.m. (EST)** if they have not received your credit card for confirmation and, if warranted, late arrival notification. If you have any questions regarding your hotel accommodations, please call Mr. Livingston.

Transportation to the Meeting

Bus transportation to the meeting has been arranged for Council members and invited speakers.

You will be transported from the hotel to the NIH campus on the morning of June 6. The bus will pick-up members at the lobby entrance of the hotel at **7:05 a.m.** at which time the NIH police will clear passengers for entrance onto the NIH campus and admittance into Building 31. The bus will depart the hotel at **7:15 a.m.** and arrive on the NIH campus **7:35 a.m.** If you miss the bus it will be necessary to have the hotel reservation desk arrange for taxi service.

Payment

You will be reimbursed for your participation in the meeting by a Professional Services Contract, (PSC), covering hotel expenses and meals and ground transportation. You will also receive an honorarium in the amount of $200.00. You will receive the reimbursement payment at the meeting.

We look forward to seeing you in June. If you have any questions or concerns, I will be pleased to assist you. I can be reached at 301-594-7232.

Mary

Mary Plummer
Committee Management Officer
Office of Committee Management, Division of Extramural Research
Eunice Kennedy Shriver National Institute
of Child Health and Human Development, NIH
6100 Executive Boulevard, Suite 5E01
Bethesda, MD 20892-7510
Tele: 301-594-7232
FAX: 301-480-2115
E-mail: plummerm@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: NIH support statement - urgent review please
Date: Tuesday, May 21, 2013 4:36:00 PM
Attachments: support statement 52113.docx

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 10:31 AM
To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Bonham, Valerie (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: NIH support statement - urgent review please

(b)(5)

Please review the attached and DO NOT LINE EDIT!! This has been reviewed by FC who is on vacation so I can't get back to him before I send this downtown. Therefore, I want only corrections of egregious errors and opinions on the places where there are retained redlines because I think they are not quite right yet.

Need this within the hour please.

Page 1370 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1371 of 2000

Withheld pursuant to exemption

(b)(5)

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Page 1372 of 2000

Withheld pursuant to exemption

(b)(5)

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Page 1373 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: NIH support statement - urgent review please
Date: Tuesday, May 21, 2013 4:28:00 PM

Yes - nice

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, May 21, 2013 4:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NIH support statement - urgent review please

Great thanks – did you see the whole statement

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, May 21, 2013 11:38 AM
To: Carr, Sarah (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

There was 1 IRB for the coordinating center and a total of 24 site IRB approvals. I believe we initially sent 23 site consents to OHRP and Mary Sharp (UCSD affiliate) was submitted later.

—Brown University
—Case Western Reserve University
—Duke University
—Emory University
—Indiana University
—Stanford University
—Tufts Medical Center
—University of Alabama – Birmingham
—University of Cincinnati –Three separate IRB's – University, Good Samaritan, Children's
—University of California – San Diego –two IRBs- UCSD and Sharp
—University of Iowa
—University of Miami
—University of New Mexico
—University of Rochester
—University of Texas, Southwestern – Dallas
—University of Texas – Houston
—University of Utah- two IRBs – University and Intermountain
—Wayne State University
—Wake Forest University
—Yale University

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higginsr@mail.nih.gov

From: Carr, Sarah (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 11:21 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

Rose, Mona,

Can one of you answer the fact check regarding the IRBs in the second paragraph – how many IRBs approved the study. Was it 22?

Thanks,

Sarah

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, May 21, 2013 10:58 AM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

Hi
For the title –"NIH and the SUPPORT Study" (nice and neutral).
I agree with (b)(5)

Cite (AAP 2007 guidelines attached)

Change -

(b)(5)

Page 2 –

(b)(5)

Thanks for including me

Rose

Rosemary D. Higgins, MD
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Need this within the hour please.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Carr, Sarah (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please
Date: Tuesday, May 21, 2013 4:04:00 PM
Attachments: RE NIH support statement - urgent review please .msg

Done

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Tuesday, May 21, 2013 4:03 PM
To: Carr, Sarah (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

Hi Sarah –did you get the answer on this one

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
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Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Carr, Sarah (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 11:21 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

Rose, Mona,

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Sarah

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Sent: Tuesday, May 21, 2013 10:58 AM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Bonham, Valerie (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

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For the title –"NIH and the SUPPORT Study" (nice and neutral).
I agree with (b)(5)

Cite (AAP 2007 guidelines attached)

Change -
(b)(5)

Page 2 –

First cite (*New England Journal of Medicine*. 2010:362;1959-1969.)

(b)(5)

Thanks for including me

Rose

Rosemary D. Higgins, MD

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Cc: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: NIH support statement - urgent review please

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Need this within the hour please.

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 2:25 PM
To: jdrazen@nejm.org
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: SUPPORT study
Attachments: support statement 52113 - klh.docx

Hi Jeff,
As Alan shared with you, NIH may be unmuzzled (at least momentarily) to share our thoughts about the SUPPORT study and what needs to happen moving forward. Attached is a draft.

After a long, tiresome, and largely failed set of negotiations between NIH and OHRP is about to send another missive to UAB and we would like to have something out there that makes clear we support the NRN and have strong disagreements with OHRP.

Frankly, I think if attached or a reasonable facsimile can come out in the pages of NEJM, HHS might not censor us.

Let us know if you have any interest and if so, what sort of timing you might be able to muster.

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

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(b)(5)

of the Freedom of Information and Privacy Act

Page 1383 of 2000

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(b)(5)

of the Freedom of Information and Privacy Act

Page 1384 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1385 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 2:18 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Briggs, Josephine (NIH/NCCAM) [E]
Subject: RE: SUPPORT study

Well, actually, they won't send the letter until we reach agreement on what nih can or can't say. I feel like (b)(5)
(b)(5)

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, May 21, 2013 2:09 PM
To: Briggs, Josephine (NIH/NCCAM) [E]
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: Re: SUPPORT study

Supposedly, OHRP will send UAB a new letter today. Kathy knows the latest.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On May 21, 2013, at 2:02 PM, "Briggs, Josephine (NIH/NCCAM) [E]" <briggsj@mail.nih.gov> wrote:

> Alan,
> Has the departmental letter on the Support study been sent out?
>
> *Josephine P. Briggs M.D*
> *Director, NCCAM*
> *National Institutes of Health*
> *9000 Rockville Pike*
> *Building 31, Room 2B11*
> *Bethesda, Maryland 20892*
> *Tel: (301) 435-6826*
> *FAX: (301) 435-6549*
> *Briggsj@mail.nih.gov*
>
> 
> <Picture (Device Independent Bitmap) 1.jpg>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Carr, Sarah (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please
Date: Tuesday, May 21, 2013 1:11:00 PM
Attachments: ND Outcome of the premature infant.pdf

http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_05.pdf

Page 15 – Period of gestation – Less than 37 weeks 523,040
Page 16 – Mortality data - Less than 37 weeks 18,703/523,040 = 3.58%; for < 32 weeks – 14,778/84,230 = 17.54%

I just got the death data from 2010-http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf

For developmental delay – depends on gestation (I have attached a nice review):
28% to 40% in infants born at 27 to 32 weeks and 45% to 50% in infants born at 22 to 26 weeks

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Cc: Carr, Sarah (NIH/OD) [E]
Subject: RE: NIH support statement - urgent review please

Hi Rose and Mona – can you help me with a couple things?

This is the opening paragraph of the statement that Kathy sent around. Can you help me with the highlighted areas?

(b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 10:31 AM
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Cc: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: NIH support statement - urgent review please

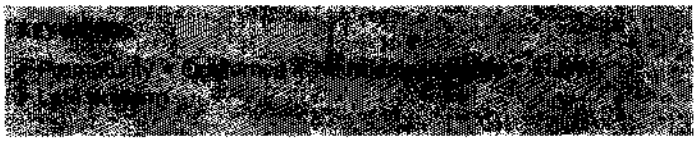
(b)(5)

Please review the attached and DO NOT LINE EDIT!! This has been reviewed by FC who is on vacation so I can't get back to him before I send this downtown. Therefore, I want only corrections of egregious errors and opinions on the places where there are retained redlines because I think they are not quite right yet.

Need this within the hour please.

Neurodevelopmental Outcome of the Premature Infant

Bonnie E. Stephens, MD[a,b,*], Betty R. Vohr, MD[a,b]



Advances in antenatal medicine and neonatal intensive care, including more aggressive delivery room resuscitation, surfactant use, antenatal corticosteroid utilization, improved ventilatory techniques, and nutritional management have successfully resulted in improved survival rates of preterm infants.[1–11] These improvements have been most dramatic in infants born extremely low birth weight (ELBW, ≤1000 g) and at the limits of viability (22 to 25 weeks).[1–3,5–8] But improvements in survival have not been accompanied by proportional reductions in the incidence of disability in this population.[2,4–7,9–15] Thus, survival is not an adequate measure of success in these infants who remain at high risk for neurodevelopmental and behavioral morbidities. The primary outcome of most neonatal clinical trials is long-term neurodevelopmental outcome.[16] Numerous authors have reported on the developmental outcomes of ELBW infants in infancy and early childhood[2,4–7,9–15,17–21] and there is now increasing evidence of sustained adverse outcomes into school age and adolescence,[22–49] not only for ELBW infants but for infants born late preterm.

EXTREMELY LOW BIRTH WEIGHT AND VERY LOW BIRTH WEIGHT INFANT SURVIVAL RATES

Survival rates for very low birth weight (VLBW; ≤1500 g) and ELBW infants consistently improved during the 1980s and 1990s.[1–4,6,9–11] The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported an improvement in the survival of all VLBW infants from 77% in 1987/1988 to 86% in 1999/2000 in their multicenter network.[1] ELBW infants in the NICHD had similar improvements in survival from 37% in 1991 to 1994 to 43% in 1995 to 1998,[3] and in a single-center report from 49% in 1982 to 1989 to 67% in 1990 to 1998.[4,12] In the early 2000s survival rates have stabilized at approximately 85% for VLBW and 70% for ELBW infants.[12,50]

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Pediatr Clin N Am 56 (2009) 631–646
doi:10.1016/j.pcl.2009.03.005 pediatric.theclinics.com

Survival remains directly proportional to gestational age and birth weight.[1,2,8,10,11,19,50–54] Although most early follow-up studies reported the outcomes of low birth weight infants weighing less than 2500 g, the improvement in survival has shifted the focus to VLBW infants weighing less than 1500 g, ELBW infants weighing less than 1000 g, and micropremies weighing less than 750 g. From 1987/1988 to 1999/2000, survival of infants weighing 500 to 750 g improved from 44% to 65%; for infants weighing 751 to 1000 g survival improved from 66% to 88%; and for 1001- to 1500-g infants from 87% to 93%, in the NICHD Neonatal Research Network.[1,8] Single centers have reported similar trends. One center reported improved survival of infants born weighing 500 to 749 g from 27% (1982 to 1989) to 48% (1990 to 1998) and infants born weighing 750 to 999 g from 66% to 85%.[4] Another center saw improvements from presurfactant use (1979 to 1985) to universal surfactant use (1989 to 1991) for all ELBW infants proportional to birth weight (500 to 599 g: 26% to 38%, 600 to 699 g: 23% to 62%, 700 to 799 g: 47% to 75%, 800 to 899 g: 63% to 82%, and 900 to 999 g: 83% to 87%). Again, survival rates have stabilized in the early 2000s, and remain directly proportional to gestational age. In a more recent NICHD report, these rates were 55% for 501- to 750-g infants, 88% for 751- to 1000-g infants, 94% for 1001- to 1250-g infants, and 96% for 1251- to 1500-g infants born 1997 to 2002.[50]

As the methodology for assessing gestational age has improved, there have been an increasing number of reports evaluating the effects of prematurity, rather than low birth weight. Preterm is defined as less than 37 weeks', very preterm is less than 32 weeks', and extremely preterm is defined as less than 28 weeks' gestation. Survival has continued to improve for even the tiniest preterm infants born at the limits of viability (22 to 25 weeks, < 800 g).[1,2,5,6] Emsley and colleagues[5] reported an increase in survival of 23- to 25-week infants from 27% (1984 to 1989) to 42% (1990 to 1994). O'Shea and colleagues[6] reported survival at 501 to 800 g improved from 20% (1979 to 1984) to 36% (1984 to 1989) to 59% (1989 to 1994) over a similar time period. In the NICHD Neonatal Research Network from 1987/1988 to 1999/2000, survival at 23 weeks improved from 23% to 30%, at 24 weeks from 34% to 59%, and at 25 weeks from 54% to 70%. For infants born weighing 501 to 600 g, survival increased from 21% to 39%; 601 to 700 g from 33% to 59%; and 701 to 800 g from 53% to 77%.[1] These survival rates vary worldwide, according to reviews of the world literature in 2000 by Hack and Fanaroff[2] and by Lorenz and colleagues.[7] Hack and Fanaroff report a range of survival at 23 weeks from 2% to 35%, at 24 weeks from 17% to 62%, and at 25 weeks from 35% to 72%; survival by birth weight varied similarly, with survival at less than 500 g ranging from 4% to 38%, 500 to 599 g from 4% to 38%, and at 600 to 699 g from 27% to 63%.[2] Lorenz and colleagues[7] reported ranges of survival by gestational age less than 26 weeks (14% to 76%) and birth weight less than 800 g (4% to 81%). Factors related to the variability in survival rates include differences in reporting (inclusion/exclusion of fetal deaths, survival to discharge home versus inclusion of postdischarge deaths), and differences in aggressiveness of antenatal and neonatal management (antenatal steroid use, cesarean section rates, delivery room resuscitation).[2] Survival rates are also consistently higher in girls than boys.[1,2,9,50,51,53] But these documented improvements in survival of VLBW and ELBW infants over the past 20 years have not been accompanied by proportional reductions in the incidence of disability in this population.[2,4–7,9–15]

NEURODEVELOPMENTAL OUTCOME

It has been almost universally accepted that neurodevelopmental outcome after preterm birth is the most important measure of neonatal ICU (NICU) success. Most

large clinical trials in the field of neonatology now include a measure of neurodevelopmental outcome. But no one optimal age of assessment has been agreed on. Because of the administrative challenges of long-term follow-up including cost, tracking, and feasibility, most authors have published data on shorter long-term outcomes (18 to 22 months corrected age). But there is now increasing evidence of adverse outcomes into school age and adolescence.[22–49]

NEURODEVELOPMENTAL IMPAIRMENT

Most published reports of neurodevelopmental outcome in infancy focus primarily on the incidence of severe disability, often defined as mental retardation, cerebral palsy, epilepsy, blindness, and/or moderate to severe hearing impairment.[2] This has historically been the neurodevelopmental outcome of interest owing to the severity of the developmental impact of these severe and often combined morbidities. Unlike mortality rates, the incidence of these moderate to severe disabilities has not changed significantly over the past 20 years.[2,4–7,9–15] Rates are highest in ELBW populations, and like mortality rates, rates of disability generally increase with decreasing gestational age and birth weight.[2,4–6,15,17,20] Hack and Fanaroff[2] report worldwide rates of severe disability in infants of 23 to 25 weeks' gestation of 34%, with rates at 24 weeks ranging from 22% to 45%, rates at 25 weeks ranging from 12% to 35%, and rates in infants born of less than 800-g birthweight of 9% to 37%. Lorenz and colleagues'[7] rates were slightly lower, with 22% disability at less than 26 weeks and 24% at less than 800 g. Factors related to the variability in reported rates of disability include variable rates of survival and neonatal complications, socioeconomic status of the population reported on, reporting on chronologic versus corrected age, variability in the definition of disability or in its clinical diagnosis, the child's age at follow-up, and variability in follow-up rates.

In the NICHD Neonatal Research Network, rates of neurodevelopmental impairment (NDI) (defined as the presence of any of the following: moderate to severe cerebral palsy, cognitive or motor scores that fall more than 2 standard deviations below the population mean on standardized testing, bilateral hearing impairment requiring amplification or bilateral blindness) in Network Centers in the 1990s ranged from 28% to 40% in infants born at 27 to 32 weeks and 45% to 50% in infants born at 22 to 26 weeks.[15] Only 21% of all ELBW infants had no impairments (no cerebral palsy, normal cognitive and motor scores, no visual or hearing impairment) at 18 months.[13] Regional and local studies in the 1990s report similar wide ranges of major neurodevelopmental impairment rates, from 20% to 48%.[4,6,9,10,12,17,37]

Center variability in outcomes is related to rates of neonatal morbidities such as sepsis, necrotizing enterocolitis, grade 3-4 intraventricular hemorrhage, and bronchopulmonary dysplasia and differences in management style including rates of administration of antenatal steroids, postnatal steroids, antibiotics, cesarean section rate, and use of ventilators.[21,55]

COGNITIVE OUTCOMES

The most common severe impairment seen in VLBW and ELBW infants at 18 and 30 months is cognitive impairment, defined as scores that are more than 2 standard deviations below the mean on standardized cognitive testing. Most follow-up studies of ELBW infants use the Bayley Scales of Infant Development II as the measure of cognitive functioning between 6 months and 3 years.[56] The Bayley has a mean score of 100 with a standard deviation of ±15. Scores of less than 70 (more than 2 standard

deviations below the mean) are considered severely impaired. When scoring a preterm infant using this assessment, corrected age (chronologic age – weeks of prematurity) is most often used until 30 months of age. Average score for ELBW infants at 18 to 22 months corrected age in the NICHD is 76[20] but varies from center to center with a range of 70 to 83.[21] Center and regional reports cite higher average MDIs. Wilson-Costello and Hack[4,10,12] report average MDIs of 84 to 86 in their cohort of infants weighing less than 1000 g born from 1982 to 2002 and 83 to 89 in a subset of infants weighing less than 750 g at 20-month follow-up. Wood and colleagues[57] reported similar results at 30 months corrected age in a cohort of 20- to 25-week infants in the United Kingdom whose average MDI was 84.

Like rates of neurodevelopmental impairment, rates of cognitive impairment vary worldwide, and are inversely proportional to gestational age and birth weight. Worldwide rates of cognitive impairment throughout childhood range from 14% to 39% at 24 weeks, 10% to 30% at 25 weeks,[2] 4% to 24% at less than 26weeks, and 11% to 18% at less than 29 weeks.[5,14] In infants born weighing less than 800 g, rates of cognitive impairment range from 13% to 50%,[2,6,7,14,19] and at less than 1250 g the rate is 26%.[14] In the NICHD, rates of cognitive impairment are reported at 37% to 47% in 22- to 26-week infants,[13,15] 23% to 30% in 27- to 32-week infants,[15] and 34% to 37% in all infants weighing less than 1000 g.[20,58] Wilson-Costello and Hack[4,10,12] site 20% to 26% rates of cognitive impairment in their cohort of ELBW infants at 18 months. At 30 months corrected age, 30% of Wood and colleagues'[57] cohort had cognitive impairment.

But cognitive functioning in infancy may not be predictive of cognitive functioning later in life. The assessment of an infant's cognitive function is highly dependent on motor, language, and social-emotional development. Thus, cognitive assessment in infancy is not as accurate as cognitive assessment later in life. In fact, Hack and colleagues[30] found that MDI at 20 months corrected age was not predictive of cognitive functioning at 8 years of age in their cohort of 330 ELBW infants. Although mean MDI at 20 months was 76, mean cognitive score at 8 years was 88. Rates of cognitive impairment dropped from 39% at 20 months to 16% at 8 years. The positive predictive value of having a low cognitive score at 8 years (<70) given a low cognitive score at 20 months (<70) was only 0.37. Ment and colleagues[33] had similar findings in a cohort of VLBW infants. Mean expressive language scores increased from 88 at 3 years to 99 at 8 years of age and full-scale IQ increased from 90 to 96.

At school age, cognitive functioning is assessed using a variety of different measures including the Stanford Binet Intelligence Scale–4th edition, the Wechsler Preschool and Primary Scales of Intelligence–3rd edition (WPPSI), the Wechsler Intelligence Scale for Children (WISC-III), the Woodcock-Johnson Psycho-Educational Battery–Revised, the Differential Abilities Scales, the McCarthy Scales of Children's Abilities, the British Abilities Scale, and the Kaufman Assessment Battery of Childhood. Each of these assessments provides an intelligence quotient (IQ) and subtest scores that allow for a limited assessment of specific areas of strengths and weaknesses. These tests, like the Bayley, have a mean of 100 with a standard deviation of 15 in the general population. Mean IQ for VLBW and ELBW infants at school age (5 to 14 years) ranges from 82 to 105.[22–24,26,27,30,33,34,41–43] Although the mean IQ is within the average or low average range for children born ELBW or VLBW, they have significantly lower IQ scores than their normal birth weight peers (0.5 to 1.0 SD lower)[22,23,26,27,31,34,41–43] and significantly higher rates of cognitive impairment.[23–25] Cognitive scores are significantly correlated with gestational age and birth weight.[22,26,28,41] Although environmental factors such as type of health insurance, bilingual household, income level, single parent, teenage mother, and level of maternal

education are known to have an impact on intelligence, differences in IQ between preterm and term controls persist after adjustment for these confounders.[59]

Although measures of intelligence in children at school age provide a reliable assessment of general cognitive functioning, they do not identify specific learning disabilities. In addition to impairments in global cognitive functioning, more subtle cognitive impairments are often detected in school age. These higher prevalence, lower severity dysfunctions reportedly occur in 50% to 70% of children born VLBW.[37] Children born VLBW or ELBW have relative impairments of executive functioning,[29,41,60,61] visual-motor skills,[61] and memory,[29,41] especially verbal memory.[32] They score lower on tests of academic achievement,[29,30,42] perceptual-organizational skills,[31,41] visual processing tasks,[31,41] and adaptive functioning[29,41] compared with their normal birth weight peers. Even ELBW infants without neurosensory or cognitive impairment have higher rates of learning disabilities,[26,27] especially in math,[31,41,43,62] ranging from 25% to 40%.[26,31]

Thus, it is not a surprise that ELBW infants have higher rates of academic underachievement and need for special education services.[25,26,34] While ELBW infants have mean scores on formal tests of academic achievement that fall within the normal range (94 to 105), they score lower than normal birth weight peers.[26,34] Teachers of VLBW infants report rates of below average school performance in all academic areas, ranging from 24% to 41%.[25,26,38,42] Approximately 25% of VLBW infants and 25% to 62% of ELBW infants receive special education services.[25,34,35,40,41,45] Between 15% and 34% required grade repetition.[35,36,41,43]

An increasing number of investigators have reported on cognitive and academic abilities of former VLBW and ELBW teenagers and young adults.[24,28,29,32,35,41,61,63] ELBW teens continue to have mean cognitive scores in the average to low average range but persist in having significantly lower cognitive and academic scores than teens born normal birth weight,[44–46] and significantly higher rates of cognitive impairment.[45,46] Cognitive differences are greatest in areas of visual-perceptual tasks.[44] Academic differences are seen in reading and mathematics.[44] As a result, only 56% to 74% of preterm children, significantly fewer than normal birth weight teens, graduate from high school.[45,46] Hack and colleagues'[46] report on a single-center cohort of VLBW infants showed significant gender differences in graduation rates: 66% of VLBW males compared with 75% for term males and 81% for VLBW females compared with 90% for term females.

MOTOR OUTCOMES

Another outcome of major concern is cerebral palsy. Extremely preterm infants are born during a period of active brain development and maturation, placing them at extremely high risk for brain injury from hypoxia, ischemia, undernutrition, and infection, which are associated with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). PVL is injury to the periventricular white matter as a result of hypoperfusion and infarction. It is visualized radiographically as echolucency, echodensity, or cystic degeneration. Although IVH, ventriculomegaly at term, and cystic PVL are all associated with cerebral palsy, cystic PVL is the strongest predictor.[64]

Cerebral palsy is typically defined as a disorder of movement and posture that involves abnormalities in tone, reflexes, coordination and movement, delay in motor milestone achievement, and aberration in primitive reflexes.[64] Rates of cerebral palsy in ELBW vary from 5% to 30%[2,4–7,10,12–15,17–21,23,24,57,64,65] but are most commonly sited at 15% to 23%.[13,15,17,20,23,24,57,64,65] The most common form of cerebral palsy in this population is spastic diplegia, accounting for 40% to 50%

of all cases, followed by spastic quadriplegia, and hemiplegia.[17,57,64] This is not surprising, as PVL lesions involve injury to the white matter that contains the descending motor tracts for the lower extremities. More extensive lesions also involve upper extremity motor tracts.

Arguably more important than the location of impairment is the functional level of the affected infant. Level of gross motor function can be assessed and categorized using Palisano's Gross Motor Function Classification System.[66] This system was developed as a method for assessment of a child's motor function by direct observation of the child's gross motor performance. It describes a child's function, not the fluidity of his or her movements. Palisano's system classifies gross motor function on a 5-point scale. Normal function at 18 to 24 months is defined as Level 0 and involves the ability to walk at least 10 steps independently. An infant at Level 1 can sit with hands free, creep or crawl on hands and knees, pull to stand, and cruise or walk with hands held. Those at Level 2 use their hands for sitting support, creep on their stomach, and may pull to stand; those at Level 3 require external support to sit, roll, and may creep; and those at Level 4 maintain head control in a supported sitting position and can roll prone to supine. Level 5 is the inability to maintain antigravity movements of the head and trunk.[64,66] Although 27% of a cohort of ELBW infants diagnosed with cerebral palsy at 18 to 22 months had moderate to severe gross motor function (Level 3 to 5), 28% had gross motor function consistent with level 0 or 1 and were ambulatory.[64] It is important to remember that a diagnosis of cerebral palsy includes a wide spectrum of motor performance.

Although cerebral palsy is the most well known and potentially most disabling motor abnormality associated with prematurity, infants born preterm often demonstrate less severe differences in their neurologic development. During the first year of life, transient dystonia is a common deviation in the motor development of VLBW infants.[67–69] Transient dystonia was first described in 1972 by Drillien[68] as transient abnormalities on neurologic examination in close to half of all low birth weight infants (<2000 g) in the first year of life. The motor features described included increased extensor tone of the trunk and lower extremities and increased adductor tone in the lower extremities leading to shoulder retraction and hip rotation, persistent primitive reflexes, head lag on pull to sit, and delayed supportive responses. These signs disappear gradually between 8 and 12 months of age in 80% of infants in which they occur. The other 20% often go on to be diagnosed with cerebral palsy. More recently these transient findings have been re-described as occurring in 21% to 36% of preterm infants with a peak incidence at 7 months corrected age.[67,69] The presence of findings consistent with dystonia increases the risk of later cognitive and motor problems including cerebral palsy but have a low specificity, as they are transient in most infants.

At school age, low birth weight infants are more likely to have subtle neurologic impairment than their normal birth weight peers.[61,70] On exam, 10% to 11% of low birth weight infants have neurologic soft signs, a twofold increased risk compared with their normal birth weight peers.[23,71] Soft signs are defined as deviations in speech, balance, coordination, gait, tone, or fine motor or visual motor tasks that do not signify localized brain dysfunction. These soft signs are associated with an increased the risk of subnormal IQ, learning disabilities, attention deficit disorder, and internalizing and externalizing behaviors at 6 and 11 years.[71]

Assessment of motor outcomes should be performed at each follow-up visit with a formal neurologic exam. Many centers use a variation of the Amiel-Tison neurologic assessment.[72] This assessment includes a standardized evaluation of muscle tone, strength, reflexes, joint angles, and posture.

NEUROSENSORY OUTCOMES

Although much less common than cognitive and motor disabilities, rates of neurosensory disabilities are higher in ELBW infants than the general population. Unilateral or bilateral blindness occurs in 1% to 10% of ELBW infants.[2,4,6,7,10,12–15,17,19–21,57] Milder visual impairments including myopia and strabismus occur at rates of 9% to 25%.[5,20,21,57]

Hearing impairment requiring amplification is reported in 1% to 9% of ELBW infants.[2,4,5,10,12–15,17,19–21,57] Milder hearing impairment has been reported in 11% to 13%,[20,57] and when transient conductive or unilateral hearing loss is included, rates of milder impairment are as high as 28%.[21] These rates of neurosensory impairment persist at school age.[23,24,40] with some studies reporting even higher rates of hearing impairment of 14%.[30]

BEHAVIORAL AND PSYCHOLOGICAL SEQUELAE

Evaluations of behavior are routinely obtained in infancy and childhood by parent, teacher, or subject interviews with standardized measures of behavior, attention, adaptive skills, and depression. The Child Behavior Checklist[73] is a questionnaire designed to describe social competencies and emotional/behavioral issues of children and is commonly used in follow-up studies. It has a version for 1.5- to 5-year-olds and a version for ages 4 to 18, which has scores that were derived for withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior, and the presence of any behavior problem. The Conners Rating Scales[74,75] are questionnaires designed for parents or teachers to describe symptoms of inattention, hyperactivity, and oppositionality in school-age children. Multiple different measures of childhood depression exist and have been studied in this population.

VLBW has been associated with a wide variety of behavioral and psychological diagnoses and disabilities. Recent concern has arisen that rates of Autism Spectrum Disorder (ASD) may be higher in ELBW infants than previously thought. Although low birth weight (< 2500 g) may result in a two- to threefold increase in the risk of ASD,[76,77] true risk of ASD in very preterm infants is unknown. Two prior studies have investigated rates of autistic characteristics in children born VLBW (<1500g). Indredavik and colleagues[48] demonstrated a trend toward higher scores on the Autism Spectrum Screening Questionnaire in a population of 56 children at 14 years of age who were born VLBW compared with full-term controls. Limperopoulos and colleagues[78] recently reported 25% of VLBW infants screen positive on the Modified Checklist for Autism in Toddlers (M-CHAT). However, the M-CHAT was developed for use in the general population and not for a high-risk population such as VLBW infants. In addition, no diagnostic confirmation was performed.[78] Further studies are needed to determine the true risk of autism in this population.

At school age (8 to 12 years old), parents and teachers of VLBW/ELBW infants report higher rates of inattention and hyperactivity,[22,25–27,36,39,41,47,48] with rates of 23% to 27% in VLBW and 33% to 37% in ELBW infants.[25,27,47,48] One quarter to one half of VLBW/ELBW infants have symptoms of anxiety and/or social withdrawal,[25,27] and at 12 to 14 years old, 8% to 14% meet criteria for generalized anxiety disorder, compared with 1% to 4% of peers.[47,48] At 12 to 14 years old, 25% to 28% of VLBWs meet criteria for a psychiatric disorder compared with 7% to 10% of peers.[47,48] At 17 and 20 years of age, ELBWs continue to score higher on measures of inattention, anxiety/depression, withdrawn behavior, and social problems.[44,49]

At 14 and 17 years of age, VLBW children score significantly lower on measures of self-esteem.[43,44] They report less confidence in their athletic, school, romantic, and job-related abilities.[44] At the age of 20 years, VLBW adults report lower rates of alcohol and drug use, sexual activity, and pregnancy than adults born normal birth weight.[46,49]

FUNCTIONAL OUTCOMES

A practical and clinically relevant approach to evaluating a child's neurodevelopment is to provide information on functional skills in daily living and health care status. Functional assessment is the process of determining a child's ability to perform the tasks of daily living and to fulfill the social roles expected of a physically and emotionally healthy child of the same age and culture. This includes tasks of feeding, dressing, bathing, maintaining continency, mobility, communication, play, and social interaction. The social roles expected include involvement with peers.

As a result of the high rates of cognitive, motor, neurosensory, and behavioral difficulties seen in children who were born VLBW, even in those without severe impairments, these children have higher rates of functional limitations than children who were born normal birth weight.[40]

Four functional outcome measures are currently available:[79–81] the Pediatric Evaluation of Disability Inventory (PEDI) for children 6 months to 7.5 years;[79] the Functional Independence Measure for Children (WeeFIM)[80,81] for children with and without disabilities through age 8 years; the Vineland Adaptive Behavior Scale (VABS), which measures communication, daily living, socialization, and motor skills in children birth to 18 years;[82] and the Battelle Developmental Inventory for children age 0 to 8 years.[83,84]

Although 93% of ELBW infants achieve sitting balance, 83% walk, and 86% feed themselves independently by 18 to 22 months corrected age, more subtle functional deficits become apparent later in life.[20] At 10 to 14 years of age, 27% of children who were VLBW and 32% of those who were ELBW report restricted physical activity; and 24% of VLBW and 29% of ELBW report they are unable to participate in sports.[40] Functional outcomes are considered particularly important by parents.

FACTORS ASSOCIATED WITH OUTCOME

Recent studies support that a combination of biologic and environmental factors contribute to survival and outcome of preterm infants. Tyson and colleagues[85] evaluated the effects of both low gestational age and gender on outcomes of ELBW infants. In a cohort of 4192 22- to 25-week gestation infants for whom the outcome was known at 18 to 22 months, 73% had died or had NDI. Factors significantly associated with an increased likelihood of a favorable outcome for infants 22- to 25-weeks' gestation who received intensive care were higher gestational age, higher birth weight, female gender, singleton, and antenatal steroids, all factors present at birth.

Multiple birth is an important risk factor for both death and NDI among VLBW infants.[18,86] In a recent NICHD Neonatal Network study, ELBW twins born from 1997 to 2005 were at increased risk of moderate to severe cerebral palsy (8.4% versus 6.3%), MDI less than 70 (39% versus 29.9%), NDI (45.1% versus 36.0%), and death or NDI (64% versus 53%) compared with singletons.[87]

Common neonatal morbidities, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity, necrotizing enterocolitis, and infection, have also been associated with poor cognitive function and academic abilities in infancy and at school age.[55,88–94] Rates of neurodevelopmental impairment at 18 to 22 months corrected age is directly proportional to duration of need for mechanical ventilation in the

NICU.[18,55] BPD has been implicated as a risk factor for cerebral palsy in multiple studies.[91–93] It also has an independent negative effect on motor outcome at 3 years.[88]

Cranial ultrasound abnormalities including severe intraventricular hemorrhage (IVH), hydrocephalus, and periventricular leukomalacia (PVL) are the strongest predictors of cerebral palsy.[91–95] Multiple authors have reported a two- to sixfold increased risk of cerebral palsy associated with grade 3 to 4 IVH,[13,15,19,93,96,97] and a 3- to 10-fold increased risk of cerebral palsy associated with cystic PVL.[13,15,19,97] The presence of hydrocephalus may increase the risk by 12.2 times,[93] and the presence of PVL and hydrocephalus by 15.4 times.[97] According to results from the Indomethacin trial, 60% of ELBW infants with grade 3 to4 IVH had cerebral palsy at 5 years of age and 92% required special services.[98]

Yet ultrasound, although helpful, lacks both sensitivity and specificity. In fact, IVH grade has been shown to account for only 5% of the variance in predicting major handicap.[92] Additionally, 6% to 9% of ELBW infants who demonstrate no abnormalities on cranial ultrasound have cerebral palsy at 18 to 22 months corrected age.[18,99] Recent studies have suggested that MRI may be more predictive of neurodevelopmental outcomes in preterm infants than cranial ultrasound.[100,101] But although MRI identifies more subtle white matter lesions than cranial ultrasound, it remains controversial whether MRI is superior in predicting outcomes.[102–105] In addition, MRI is expensive and less practical, requiring transportation and often sedation of the infant. Thus, more investigation into the identification of those individual infants who will most benefit from intervention services is needed.

LATE PRETERM

Although most neonatal outcomes research has focused on the ELBW infant, more recent studies have brought a long neglected population of infants to our attention, the late preterm population. During the 1990s the rates of delivery at 40 or more weeks' gestation decreased while rates of deliveries between 34 and 36 weeks increased steadily.[106] From 1990 to 2005 the rate of late preterm births increased from 7.3% to 9.1% of all births.[107] Compared with term infants, these late preterm infants have higher mortality rates.[108–110] They also have higher rates of neonatal morbidities such as respiratory distress, temperature instability, hypoglycemia, kernicteris, apnea, seizures, infection, and feeding problems.[107–109,111,112] All of these morbidities have the potential to have long-term neurodevelopmental sequelae. In addition, the brain of the late preterm infant is more immature than the term infant's brain. At 34 weeks there are significantly fewer gyri and sulci, and the brain weighs an estimated 60% of that of a term infant.[111] Although there is a large body of literature that addresses the neurodevelopmental outcome of VLBW and ELBW infants, there is a paucity of information published about the neurodevelopmental sequelae of late preterm birth. Infants born at 34 to 36 weeks are 3.39 times as likely as term infants to develop cerebral palsy and 1.25 times as likely to have cognitive impairment.[113] They are more likely to qualify for special needs preschool and are more likely to have problems with school readiness.[114] In kindergarten and first grade they have lower reading scores, teachers report math skills below those of their full-term peers, and they are more likely to qualify for special education services.[115]

SUMMARY

As more and more preterm infants are born and survive, more is known about their short- and long-term neurodevelopmental outcomes. Infants born preterm are at

significantly higher risk for neonatal morbidities and subsequent adverse neurologic, developmental, learning, and behavioral sequelae.

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From: Higgins, Rosemary (NIH/NICHD) [E]
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Hi
For the title –"NIH and the SUPPORT Study" (nice and neutral).
I agree with (b)(5)

Cite (AAP 2007 guidelines attached)

Change -

(b)(5)

Page 2 –

(b)(5)

Thanks for including me

Rose

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Sent: Tuesday, May 21, 2013 10:31 AM
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Subject: NIH support statement - urgent review please

(b)(5)

Please review the attached and DO NOT LINE EDIT!! This has been reviewed by FC who is on vacation so I can't get back to him before I send this downtown. Therefore, I want only corrections of egregious errors and opinions on the places where there are retained redlines because I think they are not quite right yet.

Need this within the hour please.

guidelines for

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Guidelines for Perinatal Care was developed through the cooperative efforts of the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice. The guidelines should not be viewed as a body of rigid rules. They are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

Library of Congress Cataloging-in-Publication Data

Guidelines for perinatal care / American Academy of Pediatrics [and] the American College of Obstetricians and Gynecologists. — 6th ed.
p. ; cm.
"Supported in part by March of Dimes."
Includes bibliographical references and index.
ISBN 978-1-58110-270-3 (AAP) – ISBN 978-1-932328-36-3 (ACOG)
1. Perinatology—Standards—United States. I. American Academy of Pediatrics. II. American College of Obstetricians and Gynecologists. III. March of Dimes Birth Defects Foundation.
[DNLM: 1. Perinatal Care—standards—United States—Practice Guideline. WQ 210 G955 2008]

RG600.G85 2008
618.3'2—dc22
2007015737

ISBN 978-1-58110-270-3 AAP
ISBN 978-1-932328-36-3 ACOG

Orders to purchase copies of *Guidelines for Perinatal Care* or inquiries regarding content can be directed to the respective organizations.

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Hydration

There is no evidence that excess fluid administered to the neonate decreases the serum bilirubin concentration. Some neonates who are admitted to the hospital with high bilirubin concentrations also may be mildly dehydrated and may need supplemental fluid intake to correct dehydration. In the absence of dehydration, routine supplementation (with dextrose-water) of neonates receiving phototherapy is not indicated. However, in sick, VLBW neonates receiving phototherapy, excess evaporative water loss is known to occur and frequently necessitates increased fluid intake, environmental humidity, or both for replacement or prevention of ongoing losses.

Phototherapy

Phototherapy is effective in reducing serum bilirubin concentrations in neonates with nonhemolytic jaundice. Phototherapy is less effective in neonates with ABO and CDE (Rh) group hemolytic disease, reducing, but not eliminating, the need for exchange transfusions in these neonates. Exchange transfusion is the treatment of choice when the bilirubin concentration appears to pose an imminent threat to the health of the neonate.

There is no standardized method for delivering phototherapy. However, detailed recommendations on phototherapy can be found in the hyperbilirubinemia practice parameters from the AAP. Commonly used phototherapy units contain daylight, cool white, blue, or "special blue" fluorescent tubes. Other units use tungsten-halogen lamps in different configurations, either freestanding or as part of a radiant-warming device. Fiber optic systems have been developed that deliver high-intensity light via a fiber optic blanket.

The efficacy of phototherapy is influenced by the energy output (irradiance) in the blue spectrum (measured in microwatt per centimeter squared), the spectrum of light source, and the surface area of the neonate exposed to the light source. The irradiance of a unit should be monitored and bulbs changed as needed to maintain maximum energy output. It is acceptable to interrupt phototherapy during feeding or brief parental visits. Intensive phototherapy can be achieved by use of blue lights, decreasing the distance of the source from the neonate and increasing the surface area exposed to the lights. The neonate's temperature should be monitored frequently while phototherapy is being applied.

Although phototherapy has many biologic effects, it has no known lasting toxic effects in the human neonate. Because experiments in animals have documented retinal damage from phototherapy, the neonate's eyes should be covered with opaque patches during exposure to phototherapy light. Known potential complications from improper monitoring of eye-patch placement include exposure to high-energy light, malposition and obstruction of the nares, inadequate securing of the patch that allows lid opening and resultant corneal abrasion, and conjunctivitis from use without intermittent removal to assess the condition of the covered tissues.

The determination of a neonate's suitability for early discharge requires heightened awareness of the normal course of physiologic hyperbilirubinemia. Recent data suggest that there is some predictability to the progressive increase in serum bilirubin concentrations from nonpathologic sources. It is suggested that for neonates who are otherwise candidates for early discharge, a predischarge serum bilirubin determination can be helpful in predicting risk for a subsequent increase to more concerning concentrations. A neonate with early onset jaundice (within the first 24 hours) should have hemolysis excluded as a cause before being considered for early discharge. After the newborn is discharged from the birthing hospital, the mother and child should receive a seamless continuation of care as outlined in the AAP guideline.

Some neonates with uncomplicated nonhemolytic jaundice may be treated with phototherapy at home. Guidelines should be developed by each institution to define criteria for neonates who are eligible for home phototherapy. Home care requires appropriate follow-up and supervision by a health care professional with access to serum bilirubin determinations as clinically indicated. With proper instruction of the parents or guardians, phototherapy can be provided by using a freestanding device or a fiber optic blanket. If serum bilirubin concentrations do not decrease in response to conventional phototherapy, admission to the hospital may be indicated for more intensive phototherapy or exchange transfusion and for evaluation of the underlying cause (Fig. 8–1 and Fig. 8–2).

Clinical Considerations in the Use of Oxygen

The hazards associated with nonindicated administration of supplemental oxygen to preterm neonates have been recognized for many years. Studies conducted in the 1950s indicated that prolonged oxygen therapy without clinical indication was associated with increased rates of retinopathy of prematurity, formerly called retrolental fibroplasia. The ensuing blanket restriction of ambient oxygen therapy resulted in a marked decrease in retinopathy of prematurity at the cost of an increase in morbidity and mortality. Current practice includes

the prudent use of supplemental oxygen as needed, based on an objective determination of oxygen requirements.

When supplemental oxygen therapy is considered, the potential risks, in terms of both hypoxia and hyperoxia, should be weighed. Clinical judgment of physical signs alone as a guide to the amount of supplemental oxygen needed is acceptable for short periods, emergencies, or abrupt clinical changes. However, ongoing use of supplemental oxygen should be guided by an objective assessment of patient oxygenation.

Administration and Monitoring

In an emergency, high concentrations of supplemental oxygen may be administered by a face mask, nasal prongs, or endotracheal tube. When a neonate requires oxygen therapy beyond the emergency period, the oxygen should be warmed and humidified and the concentration or flow should be monitored and regulated. Supplemental oxygen can be delivered via endotracheal tube, oxygen hood, nasal prongs, or incubator. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations. Orders for oxygen therapy should include desired ambient concentration, flow, or both. The concentration or flow rate of oxygen should be checked routinely. Alternatively, orders should be written to adjust fraction of inspired oxygen (FIO_2) or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional guideline for ordering, delivering, and documenting oxygen therapy and monitoring.

An important development in the care of neonates who require oxygen therapy is the ability to monitor oxygenation continuously with noninvasive techniques. The pulse oximeter measures oxyhemoglobin saturation and the transcutaneous oxygen analyzer provides an indirect measurement of PaO_2. Because neither technique measures PaO_2 directly, they should be used as adjuncts to, rather than substitutes for, arterial blood gas sampling, especially in neonates with moderate to severe respiratory distress.

Periodic or continuous measurement of PaO_2 in samples from an umbilical or peripheral artery catheter is the most reliable method of assessing the effectiveness of oxygen therapy. If an indwelling arterial catheter is not in place, peripheral artery puncture can be used, but this is painful and repeated sampling from these sites is not always possible. Oxygenation is not accurately estimated in arterialized capillary samples. However, arterialized capillary sampling provides fairly reliable estimates of arterial pH and $PaCO_2$. The combined use of continuous, transcutaneous oxygen saturation monitoring and intermittent

percutaneous arterial or arterialized blood gases to guide oxygen therapy is an attractive pragmatic strategy when invasive arterial catheters are not in place.

In neonates whose condition is unstable, noninvasive measurements should be correlated with PaO_2 as often as every 8–24 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and $PaCO_2$. In neonates whose condition is stable, correlation with arterial blood gas samples may be performed when clinically indicated.

The use of either pulse oximetry or transcutaneous oxygen measurement may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are particularly useful in monitoring oxygen therapy in neonates who are recovering from respiratory distress or who require long-term supplemental oxygen. Pulse oximetry is particularly advantageous for long-term monitoring of oxygen therapy because transcutaneous oxygen measurements underestimate oxygenation in older neonates with bronchopulmonary dysplasia (BPD) and may cause burns. Pulse oximetry also is widely available.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should be used for specific indications, such as cyanosis, low PaO_2, or low oxygen saturation.
- The continuous use of supplemental oxygen, other than for resuscitation, should be monitored by assessments of PaO_2, oxygen saturation, or both.
- Oxygenation monitoring should be available whenever oxygen is continuously administered to newborns.
- For neonates who require oxygen therapy for acute care, measurements of blood pH and $PaCO_2$ should accompany measurements of PaO_2. In addition, a record of blood gas measurements, noninvasive measurements of oxygenation, details of the oxygen delivery system (eg, ventilator, continuous positive airway pressure, nasal cannula, hood, mask, settings), and ambient oxygen concentrations (FIO_2, liter of flow per minute, or both) should be maintained.
- The optimal range for oxygen saturation and PaO_2 that balances tissue metabolism, growth and development, and toxicity has not been elucidated fully for preterm infants receiving supplemental oxygen. Oxygen saturation values between 85–95% and PaO_2 values between 50 mm Hg and 80 mm Hg are examples of ranges pragmatically determined by some

clinicians to guide oxygen therapy in preterm infants. Additional research to determine the "optimal" oxygenation ranges for oxygen saturation and PaO_2 is needed. Of note, even with careful monitoring, oxygen saturation and PaO_2 may fluctuate outside specified ranges, particularly in neonates with cardiopulmonary disease.

- Regular and periodic (every 1–4 hours) measurement and recording of the concentration of oxygen delivered to the neonate receiving supplemental oxygen is recommended.
- Except for an emergency situation, air–oxygen mixtures should be warmed and humidified before being administered to newborns.

Retinopathy of Prematurity

A myriad of factors, including but not limited to hyperoxia, may contribute to the pathogenesis of retinopathy of prematurity. Prematurity, low birth weight, twin gestation, severity of illness, prolonged ventilatory support (especially when accompanied by episodes of hypoxia and hypercapnia) and clinical conditions, including acidosis, shock, sepsis, apnea, anemia, chronic lung disease, intraventricular hemorrhage, patent ductus arteriosus, and vitamin E deficiency, also have been associated with retinopathy of prematurity.

To date, a safe level of PaO_2 in relation to retinopathy of prematurity has not been established. Retinopathy of prematurity has occurred in preterm neonates who have never received supplemental oxygen therapy and in neonates with cyanotic, congenital heart disease in whom PaO_2 levels never exceeded 50 mm Hg. Conversely, retinopathy of prematurity has not developed in some preterm neonates after prolonged periods of hyperoxemia. Data have demonstrated no additional progression of active prethreshold retinopathy of prematurity when supplemental oxygen was administered at pulse oximetry saturations between 96% and 99%. Further, continuous, close monitoring of transcutaneous oxygen tension has not resulted in a decrease in the incidence of retinopathy of prematurity when compared with intermittent transcutaneous monitoring. However, recent data in extremely low birth weight infants between 23 weeks and 29 weeks of gestation suggest that oxygen saturation in the lowest range (70–90%) compared with highest range (88–98%) was associated with significantly less threshold retinopathy of prematurity. A one-year follow-up showed similar neurodevelopmental outcome. Randomized, controlled-trial studies will need to be done before this lower range of oxygenation can be recommended.

On the basis of published data, the following statements regarding retinopathy of prematurity and oxygen use are warranted:

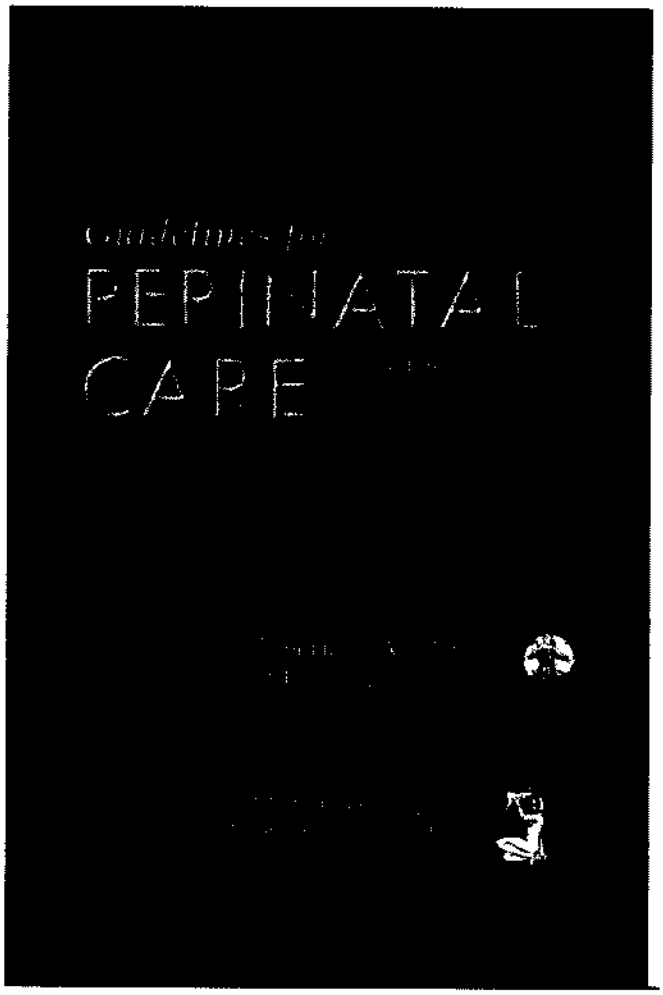
- Retinopathy of prematurity is not preventable in some neonates, especially extremely premature neonates.
- Many factors other than hyperoxia contribute to the pathogenesis of retinopathy of prematurity.
- Transient hyperoxemia alone cannot be considered sufficient to cause retinopathy of prematurity.
- Strict adherence to existing guidelines for supplemental oxygen therapy will not completely prevent complications or side effects.
- An ophthalmologist with experience in retinopathy of prematurity and indirect ophthalmoscopy should examine the retinas of all preterm neonates born at 30 weeks of gestation or less or weighing less than 1,500 g at birth, as well as selected infants between 1,500–2,000 g birth weight with an unstable clinical course who are thought to be at risk by their attending pediatrician or neonatologist. The examination should be performed at 4–6 weeks of chronologic age or at 31–33 weeks postmenstrual age (gestational age at birth plus chronologic age), as determined by the neonate's attending pediatrician or neonatologist. The use of a digital, wide-field camera system to photograph retinas of neonates at high risk is being evaluated and may prove valuable to facilitate analysis by experienced off-site ophthalmologists.
- Table 8–1 represents a suggested schedule for timing of initial eye examinations based on postmenstrual age and chronologic (postnatal) age to detect retinopathy of prematurity before it becomes severe enough to result in retinal detachment and to allow for earlier intervention, while minimizing the number of examinations, which potentially are traumatic to the baby.

The timing of follow-up examinations is best determined from the findings of the first examination, using the International Classification of Retinopathy of Prematurity. Treatment generally should be accomplished, when possible, within 72 hours of diagnosed treatable disease so as to minimize the risk of retinal detachment. The retinal findings requiring strong consideration of ablative treatment recently have been revised as follows:

—Zone I retinopathy of prematurity: any stage with plus disease

—Zone I retinopathy of prematurity: stage 3, no plus disease

—Zone II: stage 2 or 3 with plus disease



Guidelines for Perinatal Care was developed through the cooperative efforts of the American Academy of Pediatrics' (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists' (the College) Committee on Obstetric Practice. The guidelines should not be viewed as a body of rigid rules. They are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locales, the institution, or type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

Library of Congress Cataloging-in-Publication Data

Guidelines for perinatal care / American Academy of Pediatrics [and] the American College of Obstetricians and Gynecologists.—7th ed.
p. ; cm.
Perinatal care.
Includes bibliographical references and index.
ISBN 978-1-581 10-734-0 (AAP) ISBN 978-1-934984-17-8 (ACOG)
I. American Academy of Pediatrics. II. American College of Obstetricians and Gynecologists.
III. Title: Perinatal care.
[DNLM: 1. Perinatal Care—standards—United States—Practice Guideline. WQ 210]

618.3'206—dc23
2012009328

ISBN: 978-1-581 10-734-0 AAP
ISBN: 978-1-934984-17-8 the College

Orders to purchase copies of *Guidelines for Perinatal Care* or inquiries regarding content can be directed to the respective organizations:

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1 2345/6543/2

Chapter 9

Neonatal Complications and Management of High-Risk Infants

This chapter highlights some of the common complications encountered in the care of high-risk infants and, whenever possible, provides an evidence-based approach to management.

assessments using a standardized abstinence instrument.

Respiratory Complications

Oxygen Therapy

The hazards associated with administration of supplemental oxygen to preterm infants have been recognized for many years. Studies conducted in the 1950s indicated that prolonged unmonitored oxygen therapy was associated with increased rates of retinopathy of prematurity (ROP), formerly called retrolental fibroplasia. This discovery led to widespread restriction of oxygen therapy, which caused a marked decrease in ROP but an increase in cerebral palsy and mortality. Current practice recommends supplemental oxygen as needed, based on objective monitoring of oxygenation. Clinical assessment of physical signs to determine the amount of supplemental oxygen needed may be useful for short periods, emergencies, or abrupt clinical changes, but should not be the basis for ongoing supplemental oxygen therapy.

Supplemental oxygen can be delivered via endotracheal tube, mask, oxygen hood, nasal prongs, or cannula. Except in emergency situations, supplemental oxygen should be warmed and humidified, and the concentration or flow should be monitored and regulated. Orders for oxygen therapy should include desired ambient concentration, flow, or both. The concentration or flow rate of oxygen should be checked routinely. Orders should be written to adjust fraction of inspired oxygen (FIO_2) or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional guideline

for ordering, delivering, and documenting oxygen therapy and monitoring. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations.

An important development in the care of infants who require oxygen therapy is the ability to monitor oxygenation continuously with noninvasive techniques. The pulse oximeter measures the percentage of hemoglobin saturated with oxygen. Throughout most of the oxygen-hemoglobin dissociation curve, pulse oximetry will closely predict PaO_2 when adjustments are made for the presence of fetal hemoglobin, and it is an excellent continuous monitor of oxygenation; however, at saturations greater than 96%, the PaO_2 may be extremely high. The transcutaneous oxygen analyzer provides an indirect measurement of PaO_2. This device has the potential advantage of monitoring for high PaO_2; however, the heated membrane may cause burns, and the membrane may not read accurately because of poor perfusion or skin thickness, and it has been largely replaced by oximetry.

Continuous measurement of pulse oximetry combined with periodic measurement of PaO_2 in samples from an umbilical or peripheral artery catheter is the most complete method of monitoring oxygen therapy. In infants whose condition is unstable, noninvasive measurements should be correlated with PaO_2 as often as every 8–24 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and $PaCO_2$. In infants whose condition is stable, correlation with arterial blood gas samples may be performed when clinically indicated.

In the absence of an indwelling arterial catheter, arterialized capillary sampling provides reasonable estimates of arterial pH and $PaCO_2$ if perfusion to the extremity is not compromised. Although PaO_2 is not accurately estimated in arterialized capillary samples, the combined use of continuous oxygen saturation monitoring and intermittent capillary arterialized blood gases can guide oxygen therapy. In this circumstance, oxygen saturation should not be allowed to remain above 95%, as previously described, particularly in preterm infants at risk of ROP.

The use of either pulse oximetry or transcutaneous oxygen measurement may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are also useful in monitoring oxygen therapy in infants who are recovering from respiratory distress or who require long-term supplemental oxygen. Pulse oximetry is particularly advantageous for long-term monitoring of oxygen therapy

because transcutaneous oxygen measurements underestimate oxygenation in older infants with BPD and may cause burns.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should be used for specific indications, such as cyanosis, low Pa_{O_2}, or low oxygen saturation.
- For infants who require oxygen therapy for acute care, measurements of blood pH and $PaCO_2$ should accompany measurements of Pa_{O_2}. In addition, a record of blood gas measurements, noninvasive measurements of oxygenation, details of the oxygen delivery system (eg, ventilator, continuous positive airway pressure, nasal cannula, hood, mask, settings), and ambient oxygen concentrations (FI_{O_2}, liter of flow per minute, or both) should be maintained.
- The optimal range for oxygen saturation and Pa_{O_2} that balances tissue metabolism, growth and development, and toxicity has not been elucidated for preterm infants receiving supplemental oxygen. Data from cohort studies initially suggested that lower saturation ranges may decrease ROP. However, three RCTs demonstrated that although a target saturation range of 85–89% was associated with a decrease in severe ROP, it also was associated with an increase in mortality, compared with a target saturation range of 91–95%. These findings resulted in early study closure of two of these three studies, and a recommendation to target a saturation range higher than 85–89%. Of note, even with careful monitoring, oxygen saturation and Pa_{O_2} often fluctuate outside specified ranges, particularly in infants with cardiopulmonary disease.
- Regular and periodic (every 1–4 hours) measurement and recording of the concentration of oxygen delivered to the infant receiving supplemental oxygen is recommended.
- Except for an emergency situation, air–oxygen mixtures should be warmed and humidified before being administered to infants.

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is associated with surfactant deficiency and typically occurs in preterm infants, but may occasionally be seen in term infants, particularly in the setting of maternal diabetes. Multiple randomized controlled trials have demonstrated the benefits of surfactant replacement therapy, including reduction in the severity of RDS, decrease in pulmonary complications (eg, air leak), and improvement in survival. Surfactant therapy does not change

Oxygenation (see also "Hydration" in Chapter 6)

Retinopathy of Prematurity

A myriad of factors, including but not limited to hyperoxia, may contribute to the pathogenesis of ROP. Prematurity; low birth weight; multiple gestation; severity of illness; prolonged ventilatory support (especially when accompanied by episodes of hypoxia and hypercapnia); and clinical conditions, including acidosis, shock, sepsis, apnea, anemia, chronic lung disease, intraventricular hemorrhage, patent ductus arteriosus, and vitamin E deficiency also have been associated with retinopathy of prematurity.

To date, a safe level of PaO_2 in relation to retinopathy of prematurity has not been established, perhaps because multiple other factors, such as those listed previously play a part in its pathogenesis. Retinopathy of prematurity has occurred in preterm infants who have never received supplemental oxygen therapy and in infants with cyanotic congenital heart disease in whom PaO_2 levels never exceeded 50 mm Hg. Conversely, ROP has not developed in some preterm infants after prolonged periods of hyperoxemia. Data have demonstrated no additional progression of active prethreshold retinopathy of prematurity when supplemental oxygen was administered at pulse oximetry

saturations between 96% and 99%. Further, continuous, close monitoring of transcutaneous oxygen tension has not resulted in a decrease in the incidence of ROP when compared with intermittent transcutaneous monitoring. On the basis of published data, the following statements regarding ROP and oxygen use are warranted:

- Retinopathy of prematurity is not preventable in some infants, especially extremely premature infants.
- Many factors other than hyperoxia contribute to the pathogenesis of retinopathy of prematurity.
- Transient hyperoxemia alone cannot be considered sufficient to cause retinopathy of prematurity.
- Strict adherence to existing guidelines for supplemental oxygen therapy will not completely prevent complications or adverse effects.

Screening and Initial Examination

An ophthalmologist with sufficient knowledge and experience in retinopathy of prematurity and the use of binocular indirect ophthalmoscopy should examine the retinas of all preterm infants born at 30 weeks of gestation or less or weighing less than 1,500 g at birth, as well as selected infants weighing 1,500–2,000 g at birth with an unstable clinical course and who are thought to be at risk by their attending pediatrician or neonatologist. Sterile instruments should be used to examine each infant in order to avoid possible cross contamination of infectious agents. Pretreatment of the eyes with a topical anesthetic agent, such as proparacaine may minimize the discomfort and systemic effect of this examination. Consideration also may be given to the use of nonpharmacologic pain management interventions, such as pacifiers and oral sucrose.

Table 9-3 presents a suggested schedule for timing of initial eye examinations based on postmenstrual age and chronologic (postnatal) age. This schedule was designed to detect retinopathy of prematurity before it progresses to retinal detachment and to allow for earlier intervention, while minimizing the number of potentially traumatic examinations. The timing of follow-up examinations is best determined from the findings of the first examination, using the International Classification of Retinopathy of Prematurity (see also "Treatment and Follow-up Care" later in this section). One examination is sufficient only if it unequivocally shows the retina to be fully vascularized in each eye.

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From: Higgins, Rosemary (NIH/NICHD) [E]
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Here you go – I added several slides on NRN productivity.

Thanks
Rose

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On May 20, 2013, at 4:25 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi
> I have prepared slides for the upcoming June 6 council meeting. Pease note – slides 11 and 12 may be subject to change if there is any further correspondence with OHRP. I would also like to share it with Dr. Wally Carlo before the end of the week to alleviate overlap in the two presentations.
>
> Thanks for your help and support.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: NICHDWorkflow
Sent: Monday, May 20, 2013 4:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Clearance Tracking: Presentation Clearance Request Awaiting Your Action

The following request for clearance is awaiting your action: Request ID: 11476 Request Type: Presentation Title: SUPPORT TRIAL Requestor: NIH\higginsr Branch/Center/Division: DER / PPB Status: Requestor Edits You may access the system at: http://insider.nichd.nih.gov/clearancetracking

<SUPPORT Council 2013-06-06.potx>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Clearance Tracking: Presentation Clearance Request Awaiting Your Action
Date: Tuesday, May 21, 2013 9:32:00 AM

Thanks
Mona also suggested I add a (b)(5)
(b)(5)

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Sent: Tuesday, May 21, 2013 9:32 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: Re: Clearance Tracking: Presentation Clearance Request Awaiting Your Action

Rose, I have a few suggested edits. Can't do on BB, but will do later this evening. Thanks

---

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, May 20, 2013 04:25 PM
To: Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: FW: Clearance Tracking: Presentation Clearance Request Awaiting Your Action

Hi
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Thanks for your help and support.

Rose

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From: NICHDWorkflow
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To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Clearance Tracking: Presentation Clearance Request Awaiting Your Action

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Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 21, 2013 7:31 AM
To: Collins, Francis (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Re: DRAFT outline- HHS stmt on SUPPORT

We are clear to have a statement and so pls pls look at what I sent.

HHS statement is in addition to our statement on support. Recall we were considering (b)(5) (b)(5) I am proposing (b)(5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 20, 2013, at 10:52 PM, "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov> wrote:

> Hi Kathy,
>
> Just logging on after an evening at the Non Responsive Non Responsive
>
> On to business – I'm not quite sure from the e-mail thread where things stand with the various statements on SUPPORT. I agree that it would be (b)(5) (b)(5) (b)(5) Has there been some phone discussion about this?
>
> And what does this do to the NIH statement that you forwarded earlier? Do you want me to take a crack at editing, or is that on hold now?
>
> FC
>
> **From:** Hudson, Kathy (NIH/OD) [E]
> **Sent:** Monday, May 20, 2013 6:08 PM
> **To:** Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]
> **Subject:** Fwd: DRAFT outline- HHS stmt on SUPPORT
>
> If HHS is willing to (b)(5) (b)(5)
>
> Kathy Hudson, Ph.D.
> Deputy Director for Science, Outreach, and Policy
> NIH

301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

From: "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov>
Date: May 20, 2013, 5:43:29 PM EDT
To: "Jones, Wanda K. (DHHS/OS/OASH)" <Wanda.Jones@hhs.gov>, "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>, "Menikoff, Jerry (HHS/OASH)" <Jerry.Menikoff@hhs.gov>, "Bradley, Ann (HHS/OASH)" <Ann.Bradley@hhs.gov>
Cc: "Sye, Tait (OS/ASPA)" <Tait.Sye@hhs.gov>, "Dotzel, Peggy (HHS/OGC)" <Peggy.Dotzel@hhs.gov>, "Wolters, Bradley (OS/OPHS)" <Bradley.Wolters@hhs.gov>, "Koh, Howard (HHS/OASH)" <Howard.Koh@hhs.gov>, "Bumpus, Kirby (HHS/OASH)" <Kirby.Bumpus@hhs.gov>
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

Our thoughts at this time is that this would be an HHS activity.

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, May 20, 2013 5:21 PM
To: Lewis, Caya (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

IOM, then? Does HHS fund it?

A high-level statement, sure, but it would be good to have some idea of the sort of venue/placement—all will have pros and cons—and that may help us be clearer about the 'who, what, where' sorts of questions that will naturally arise.

From: Lewis, Caya (HHS/IOS)
Sent: Monday, May 20, 2013 5:02 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

Thanks Wanda. We've (b)(5)

(b)(5)

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, May 20, 2013 4:54 PM
To: Lewis, Caya (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH);

Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: RE: DRAFT outline- HHS stmt on SUPPORT

Why not use SACHRP, which is a Secretarial Advisory Committee? Although OHRP manages them, they're neither a rubber-stamp nor a slam dunk for OHRP's activities.

Their meeting is forum in which experts could be invited, under FACA open-meeting rules, and they can issue recommendations without needing to be specially charged to do so. They're already scheduled to meet in July, and I don't believe an agenda is set—my guess is, they themselves will be divided on this issue, and will very much want to tackle it. Convening another group of experts likely would take far longer to organize and schedule.

From: Lewis, Caya (HHS/IOS)
Sent: Monday, May 20, 2013 4:39 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Menikoff, Jerry (HHS/OASH); Bradley, Ann (HHS/OASH)
Cc: Sye, Tait (OS/ASPA); Dotzel, Peggy (HHS/OGC); Wolters, Bradley (OS/OPHS); Koh, Howard (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Subject: DRAFT outline- HHS stmt on SUPPORT
Importance: High

All,

As OHRP is finalizing their letter to UAB, (b)(5)

(b)(5)

concerns.

Thanks,

Caya

(b)(5)

Page 1428 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: 6.6.2013 SUPPORT Council.potx
Date: Monday, May 20, 2013 3:51:00 PM
Attachments: 6.6.2013 SUPPORT Council.potx

From: Wally Carlo, M.D.
To: Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Cunningham, Meg
Subject: RE: Jack Sinclair
Date: Monday, May 20, 2013 9:36:39 AM

He has not sent a proposal. He wants the forms to prepare a proposal.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, May 20, 2013 8:32 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Cunningham, Meg
Subject: RE: Jack Sinclair

HI,

Can you please send his proposal or approved request.

Thanks,
KRIs

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Monday, May 20, 2013 9:27 AM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; wacarlo@uab.edu
Cc: Cunningham, Meg
Subject: RE: Jack Sinclair

So 2006-2009 SUPPORT and GDB form and 2007-2012 FU forms (no protocols or manuals), correct?

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, May 20, 2013 9:23 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; wacarlo@uab.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
Subject: RE: Jack Sinclair

Correct.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
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1700 6th Avenue South
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, May 20, 2013 8:21 AM
To: 'Zaterka-Baxter, Kristin'; Wally Carlo, M.D.; wacarlo@uab.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
Subject: RE: Jack Sinclair

He wants the ones over the time course of SUPPORT, right?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, May 20, 2013 9:20 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg
Subject: RE: Jack Sinclair

Morning,

Should we release the latest version of all forms?

Thanks,
Kris

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, May 20, 2013 8:53 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu)

Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: Re: Jack Sinclair

Rose.

Sure. Please do. Thanks so much.

Wally

-----Original message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>
Cc: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, " (kzaterka@rti.org)" <kzaterka@rti.org>, " (mcunningham@rti.org)" <mcunningham@rti.org>
Sent: Mon, May 20, 2013 12:39:35 GMT+00:00
Subject: Jack Sinclair

Wally – the request for Jack Sinclair to receive the GDB and FU forms was approved. Would you like us to send to him?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Cc: Cunningham, Meg
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Date: Monday, May 20, 2013 9:36:00 AM

SUPPORT enrolled from 2005-9. Protocol and manual are not needed.

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Edwin M. Dixon Professor of Pediatrics
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Sent: Monday, May 20, 2013 9:20 AM
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Kris

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Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg
Subject: Re: Jack Sinclair

Rose.

Sure. Please do. Thanks so much.

Wally

-----Original message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>
Cc: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, " (kzaterka@rti.org)" <kzaterka@rti.org>, " (mcunningham@rti.org)" <mcunningham@rti.org>

Sent: Mon, May 20, 2013 12:39:35 GMT+00:00
Subject: Jack Sinclair

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Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Monday, May 20, 2013 7:15 AM
To: Michael Carome
Cc: Ruth Macklin (ruth.macklin@einstein.yu.edu); Hudson, Kathy (NIH/OD) [E]; Sidney Wolfe; Collins, Francis (NIH/OD) [E]
Subject: Re: Copy of Letter

Thank you.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On May 20, 2013, at 6:58 AM, "Michael Carome" <mcarome@citizen.org> wrote:

> Alan,
>
> To facilitate your sharing of the letter we hand-delivered on Friday, here is an electronic copy of it.
>
> Mike
>
> Michael A. Carome, M.D.
> Deputy Director, Health Research Group
> Public Citizen
> 1600 20th Street, NW
> Washington, DC 20009
>
> Tele: 202-588-7781
> Fax: 202-588-7796
> email: mcarome@citizen.org
> web: www.citizen.org
>
> <130517_Letter to NICHD Director Requesting SUPPPORT Data_FINAL.pdf>

Blansfield, Earl (NIH/NICHD) [E]

From: Michael Carome <mcarome@citizen.org>
Sent: Monday, May 20, 2013 6:59 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: 'Ruth Macklin (ruth.macklin@einstein.yu.edu)'; Hudson, Kathy (NIH/OD) [E]; Sidney Wolfe; Collins, Francis (NIH/OD) [E]
Subject: Copy of Letter
Attachments: 130517_Letter to NICHD Director Requesting SUPPPORT Data_FINAL.pdf

Alan,

To facilitate your sharing of the letter we hand-delivered on Friday, here is an electronic copy of it.

Mike

Michael A. Carome, M.D.
Deputy Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

May 17, 2013

Alan E. Guttmacher, M.D.
Director, National Institute of Child Health and Human Development
National Institutes of Health
Building 31, Room 2A03
9000 Rockville Pike
Bethesda, Maryland 20892

RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)

Dear Dr. Guttmacher:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to request a digital copy of all individual subject-level data — without subject identifiers — obtained for the SUPPORT study that was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. We are seeking data for (a) the 1,312 subjects enrolled and randomly assigned to one of the four experimental groups in the SUPPORT study; and (b) those subjects who were eligible to be, but were not, enrolled in the SUPPORT study, and for whom data was collected and published regarding demographics, baseline clinical characteristics, and clinical outcomes.[1] We also urge you to make this data publicly available for further analysis by other independent researchers.

Thank you for your prompt attention to this request. Please notify us immediately if you have any questions about the data we are seeking or anticipate problems fulfilling our request.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

cc: Dr. Francis Collins, Director, National Institutes of Health

[1] Rich W, Finer NN, Gantz MG, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics.* March 2012;129(3):480-484.

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Saturday, May 18, 2013 2:40 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: NIH two pager SUPPORT - Revised 042513 1115 rh
Attachments: NIH two pager SUPPORT - Revised 042513 1115 rh.docx

I completely forgot about his document. Maybe we should just tweak this and use it as the statement from nih when the uab letter goes.

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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1441 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1442 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1443 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Wally Carlo, M.D.

To: Higgins, Rosemary (NIH/NICHD) [E]; "AnnaMaria.hibbs@cwru.edu"; "Jon.E.Tyson@uth.tmc.edu"; "KIRPALANIH@email.chop.edu"; "Kathleen.A.Kennedy@uth.tmc.edu"; "Leif.Nelin@nationwidechildrens.org"; "Pablo.Sanchez@UTSouthwestern.edu"; "UDEVASKAR@MEDNET.UCLA.EDU"; "adas@rti.org"; "alaptook@wihri.org"; "ambal@uab.edu"; "barbara.schmidt@uphs.upenn.edu"; "barbara_stoll@oz.ped.emory.edu"; "bcoindex@iupui.edu"; "bsood@med.wayne.edu"; "carl_dangio@urmc.rochester.edu"; "cotte010@mc.duke.edu"; "dpcarlt@emory.edu"; "dstevenson@stanford.edu"; "dwallace@rti.org"; "edward-bell@uiowa.edu"; "goldb008@mc.duke.edu"; "gsokol@iupui.edu"; "jbarks@med.umich.edu"; "kurt.schibler@cchmc.org"; "kwatterberg@salud.unm.edu"; "luc.brion@utsouthwestern.edu"; "mcw3@po.cwru.edu"; "mgarg@mednet.ucla.edu"; "mkeszler@wihri.org"; "rap32@mail.cumc.columbia.edu"; "rohls@salud.unm.edu"; "ronnie_guillet@urmc.rochester.edu"; "slakshmi@buffalo.edu"; "sshankar@med.wayne.edu"; "suhas.kallapur@cchmc.org"; "vanmeurs@stanford.edu"; "wacarlo@uab.edu"; "wtruog@cmh.edu"; "Aasma.Chaudhary@uphs.upenn.edu"; "CBackstrom@salud.unm.edu"; "Christine.Fortney@nationwidechildrens.org"; "Deanna_Maffett@urmc.rochester.edu"; "Diana.Vasil@utsouthwestern.edu"; "Georgia.E.McDavid@uth.tmc.edu"; "Holly_Wadkins@urmc.rochester.edu"; "JF126@notes.duke.edu"; "Kimberley.fisher@duke.edu"; "Lijun.Chen@UTSouthwestern.edu"; "Rosemary_Jensen@urmc.rochester.edu"; "ahensman@wihri.org"; "cagauldin@cmh.edu"; "cathy.grisby@uc.edu"; "dhwilson@iupui.edu"; "donia-campbell@uiowa.edu"; "ellen_hale@oz.ped.emory.edu"; "karen-johnson@uiowa.edu"; "kwynn@upa.chob.edu"; "ldw@iupui.edu"; "linda_reubens@urmc.rochester.edu"; "mbball@leland.stanford.edu"; Monica.Collins; "nxs5@cwru.edu"; "rbara@med.wayne.edu"; "rgeller.mednet.ucla@gmail.com"; "rgeller@mednet.ucla.edu"; "shigdon@med.umich.edu"; "tchanlaw@ucla.edu"; "Lizette.Torres@UTSouthwestern.edu"; "Margaret.Poundstone@uth.tmc.edu"; Vivien Phillips; "afurey@tuftsmedicalcenter.org"; "bss5@case.edu"; "dbeilby22@msn.com"; "diane-eastman@uiowa.edu"; "diane_hust@URMC.Rochester.edu"; "ehale@emory.edu"; "elaine.romano@yale.edu"; "igabrio@rti.org"; "jwereszc@med.unc.edu"; "karen.osborne@hsc.utah.edu"; "kzaterka@rti.org"; "ldrichar@iupui.edu"; "lohme001@mc.duke.edu"; "mcunningham@rti.org"; "mgfuller@ucsd.edu"; "newman@rti.org"; "petrie@rti.org"; "sgbrown@salud.unm.edu"; "smc48@notes.duke.edu"; "teresa.gratton@uc.edu"; "EMcGowan@tufts-nemc.org"; "JaFuller@salud.unm.edu"; "Keith.Yeates@nationwidechildrens.org"; "Kimberly.Yolton@cchmc.org"; Myriam Peralta, M.D.; "Patricia.W.Evans@uth.tmc.edu"; "Roy.Heyne@utsouthwestern.edu"; "apappas@med.wayne.edu"; "bvohr@wihri.org"; "diane_marshall@med.unc.edu"; "drfrigmd@aol.com"; "gary_myers@URMC.Rochester.edu"; "gerdes@email.chop.edu"; "golds005@mc.duke.edu"; "hkilbride@cmh.edu"; "hurt@email.chop.edu"; "jadamsc@emory.edu"; "jourdy@mednet.ucla.edu"; "jennifer.benjamin@yale.edu"; "michael-acarrequi@uiowa.edu"; "richard.ehrenkranz@yale.edu"; "rtyler@mednet.ucla.edu"; "soraya.abbasi@uphs.upenn.edu"; "srhintz@stanford.edu"; "tarah-colaizy@uiowa.edu"; "yvaucher@ucsd.edu"; Archer, Stephanie (NIH/NICHD) [E]

Subject: Keith Barrington"s blogs

Date: Friday, May 17, 2013 11:58:55 PM

Just wanted to share Keith's blogs.

I enjoyed reading them.

Have a great weekend.

Wally
http://neonatalresearch.org/2013/04/16/now-we-will-have-to-know-the-results-of-our-research-before-we-start-the-study/

http://neonatalresearch.org/2013/04/16/how-to-show-you-dont-understand-research-in-critical-patients/

http://neonatalresearch.org/2013/04/16/no-ethical-breakdown-here/

http://neonatalresearch.org/2013/04/20/even-more-supportive/

http://neonatalresearch.org/2013/04/25/more-support-for-support/

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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, May 06, 2013 8:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'AnnaMaria.hibbs@cwru.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'KIRPALANHI@email.chop.edu'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Leif.Nelin@nationwidechildrens.org'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'UDEVASKAR@MEDNET.UCLA.EDU'; 'adas@rti.org'; 'alaptook@wihri.org'; 'ambal@uab.edu'; 'barbara.schmidt@uphs.upenn.edu'; 'barbara_stoll@oz.ped.emory.edu'; 'bpoindex@iupui.edu'; 'bsood@med.wayne.edu'; 'carl_dangio@urmc.rochester.edu'; 'cotte010@mc.duke.edu'; 'dpcarlt@emory.edu'; 'dstevenson@stanford.edu'; 'dwallace@rti.org'; 'edward-bell@uiowa.edu'; 'goldb008@mc.duke.edu'; 'gsokol@iupui.edu'; 'jbarks@med.umich.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'luc.brion@utsouthwestern.edu'; 'mcw3@po.cwru.edu'; 'mgarg@mednet.ucla.edu'; 'mkeszler@wihri.org'; 'rap32@mail.cumc.columbia.edu'; 'rohls@salud.unm.edu'; 'ronnie_guillet@urmc.rochester.edu'; 'slakshmi@buffalo.edu'; 'sshankar@med.wayne.edu'; 'suhas.kallapur@cchmc.org'; 'vanmeurs@stanford.edu'; 'wacarlo@uab.edu'; 'wtruog@cmh.edu'; 'Aasma.Chaudhary@uphs.upenn.edu'; 'CBackstrom@salud.unm.edu'; 'Christine.Fortney@nationwidechildrens.org'; 'Deanna_Maffett@urmc.rochester.edu'; 'Diana.Vasil@utsouthwestern.edu'; 'Georgia.E.McDavid@uth.tmc.edu'; 'Holly_Wadkins@urmc.rochester.edu'; 'JF126@notes.duke.edu'; 'Kimberley.fisher@duke.edu'; 'Lijun.Chen@UTSouthwestern.edu'; 'Rosemary_Jensen@urmc.rochester.edu'; 'ahensman@wihri.org'; 'cagauldin@cmh.edu'; 'cathy.grisby@uc.edu'; 'dhwilson@iupui.edu'; 'donia-campbell@uiowa.edu'; 'ellen_hale@oz.ped.emory.edu'; 'karen-johnson@uiowa.edu'; 'kwynn@upa.chob.edu'; 'ldw@iupui.edu'; 'linda_reubens@urmc.rochester.edu'; 'mbball@leland.stanford.edu'; Monica Collins; 'nxs5@cwru.edu'; 'rbara@med.wayne.edu'; 'rgeller.mednet.ucla@gmail.com'; 'rgeller@mednet.ucla.edu'; 'shigdon@med.umich.edu'; 'tchanlaw@ucla.edu'; 'Lizette.Torres@UTSouthwestern.edu'; 'Margaret.Poundstone@uth.tmc.edu'; Vivien Phillips; 'afurey@tuftsmedicalcenter.org'; 'bss5@case.edu'; 'dbeilby22@msn.com'; 'diane-eastman@uiowa.edu'; 'diane_hust@URMC.Rochester.edu'; 'chale@emory.edu'; 'elaine.romano@yale.edu'; 'jgabrio@rti.org'; 'jwereszc@med.unc.edu'; 'karen.osborne@hsc.utah.edu'; 'kzaterka@rti.org'; 'ldrichar@iupui.edu'; 'lohme001@mc.duke.edu'; 'mcunningham@rti.org'; 'mgfuller@ucsd.edu'; 'newman@rti.org'; 'petrie@rti.org'; 'sgbrown@salud.unm.edu'; 'smc48@notes.duke.edu'; 'teresa.gratton@uc.edu'; 'EMcGowan@tufts-nemc.org'; 'JaFuller@salud.unm.edu'; 'Keith.Yeates@nationwidechildrens.org'; 'Kimberly.Yolton@cchmc.org'; Myriam Peralta, M.D.; 'Patricia.W.Evans@uth.tmc.edu'; 'Roy.Heyne@utsouthwestern.edu'; 'apappas@med.wayne.edu'; 'bvohr@wihri.org'; 'diane_marshall@med.unc.edu'; 'drtjcmd@aol.com'; 'gary_myers@URMC.Rochester.edu'; 'gerdes@email.chop.edu'; 'golds005@mc.duke.edu'; 'hkilbride@cmh.edu'; 'hurt@email.chop.edu'; 'iadamsc@emory.edu'; 'ipurdy@mednet.ucla.edu'; 'jennifer.benjamin@yale.edu'; 'michael-acarregui@uiowa.edu'; 'richard.ehrenkranz@yale.edu'; 'rtyler@mednet.ucla.edu'; 'soraya.abbasi@uphs.upenn.edu'; 'srhintz@stanford.edu'; 'tarah-colaizy@uiowa.edu'; 'yvaucher@ucsd.edu'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Sad news

Here is Karen's Address:

(b)(6)

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, May 06, 2013 7:37 PM
To: 'AnnaMaria.hibbs@cwru.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'KIRPALANIH@email.chop.edu'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Leif.Nelin@nationwidechildrens.org'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'UDEVASKAR@MEDNET.UCLA.EDU'; 'adas@rti.org'; 'alaptook@wihri.org'; 'ambal@uab.edu'; 'barbara.schmidt@uphs.upenn.edu'; 'barbara_stoll@oz.pcd.emory.edu'; 'bpoindex@iupui.edu'; 'bsood@med.wayne.edu'; 'carl_dangio@urmc.rochester.edu'; 'cotte010@mc.duke.edu'; 'dpearlt@emory.edu'; 'dstevenson@stanford.edu'; 'dwallace@rti.org'; 'edward-bell@uiowa.edu'; 'goldb008@mc.duke.edu'; 'gsokol@iupui.edu'; 'jbarks@med.umich.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'luc.brion@utsouthwestern.edu'; 'mcw3@po.cwru.edu'; 'mgarg@mednet.ucla.edu'; 'mkeszler@wihri.org'; 'rap32@mail.cumc.columbia.edu'; 'rohls@salud.unm.edu'; 'ronnie_guillet@urmc.rochester.edu'; 'slakshmi@buffalo.edu'; 'sshankar@med.wayne.edu'; 'suhas.kallapur@cchmc.org'; 'vanmeurs@stanford.edu'; 'wacarlo@uab.edu'; 'wtruog@cmh.edu'; 'Aasma.Chaudhary@uphs.upenn.edu'; 'CBackstrom@salud.unm.edu'; 'Christine.Fortney@nationwidechildrens.org'; 'Deanna_Maffett@urmc.rochester.edu'; 'Diana.Vasil@utsouthwestern.edu'; 'Georgia.E.McDavid@uth.tmc.edu'; 'Holly_Wadkins@urmc.rochester.edu'; 'JF126@notes.duke.edu'; 'Kimberley.fisher@duke.edu'; 'Lijun.Chen@UTSouthwestern.edu'; 'MGarg@mednet.ucla.edu'; 'Rosemary_Jensen@urmc.rochester.edu'; 'ahensman@wihri.org'; 'cagauldin@cmh.edu'; 'cathy.grisby@uc.edu'; 'dhwilson@iupui.edu'; 'donia-campbell@uiowa.edu'; 'ellen_hale@oz.ped.emory.edu'; 'karen-johnson@uiowa.edu'; 'kwynn@upa.chob.edu'; 'ldw@iupui.edu'; 'linda_reubens@urmc.rochester.edu'; 'mbball@leland.stanford.edu'; 'mcollins@peds.uab.edu'; 'nxs5@cwru.edu'; 'rbara@med.wayne.edu'; 'rgeller.mednet.ucla@gmail.com'; 'rgeller@mednet.ucla.edu'; 'shigdon@med.umich.edu'; 'tchanlaw@ucla.edu'; 'JF126@notes.duke.edu'; 'Lizette.Torres@UTSouthwestern.edu'; 'Margaret.Poundstone@uth.tmc.edu'; 'Rosemary_Jensen@urmc.rochester.edu'; 'VPhillips@peds.uab.edu'; 'afurey@tuftsmedicalcenter.org'; 'bss5@case.edu'; 'dbeilby22@msn.com'; 'diane-eastman@uiowa.edu'; 'diane_hust@URMC.Rochester.edu'; 'chale@emory.edu'; 'elaine.romano@yale.edu'; 'jgabrio@rti.org'; 'jwereszc@med.unc.edu'; 'karen.osborne@hsc.utah.edu'; 'kimberley.fisher@duke.edu'; 'kzaterka@rti.org'; 'ldrichar@iupui.edu'; 'lohme001@mc.duke.edu'; 'mcunningham@rti.org'; 'mgfuller@ucsd.edu'; 'newman@rti.org'; 'petrie@rti.org'; 'sgbrown@salud.unm.edu'; 'smc48@notes.duke.edu'; 'teresa.gratton@uc.edu'; 'EMcGowan@tufts-nemc.org'; 'JaFuller@salud.unm.edu'; 'Keith.Yeates@nationwidechildrens.org'; 'Kimberly.Yolton@cchmc.org'; 'MPeralta@PEDS.UAB.EDU'; 'Patricia.W.Evans@uth.tmc.edu'; 'Roy.Heyne@utsouthwestern.edu'; 'apappas@med.wayne.edu'; 'bpoindex@iupui.edu'; 'bvohr@wihri.org'; 'diane_marshall@med.unc.edu'; 'drfjcmd@aol.com'; 'gary_myers@URMC.Rochester.edu'; 'gerdes@email.chop.edu'; 'golds005@mc.duke.edu'; 'hkilbride@cmh.edu'; 'hurt@email.chop.edu'; 'iadamsc@emory.edu'; 'ipurdy@mednet.ucla.edu'; 'jennifer.benjamin@yale.edu'; 'jgabrio@rti.org'; 'kzaterka@rti.org'; 'mcunningham@rti.org'; 'michael-acarregui@uiowa.edu'; 'newman@rti.org'; 'petrie@rti.org'; 'richard.ehrenkranz@yale.edu'; 'rtyler@mednet.ucla.edu'; 'soraya.abbasi@uphs.upenn.edu'; 'srhintz@stanford.edu'; 'tarah-colaizy@uiowa.edu'; 'yvaucher@ucsd.edu'; 'mcunningham@rti.org'; 'kzaterka@rti.org'; 'newman@rti.org'; 'jgabrio@rti.org'; Archer, Stephanie (NIH/NICHD) [E]; 'petrie@rti.org'
Subject: Sad news

Hi,
As many of you know, (b)(6)

(b)(6)

I will send Karen's address later tonight.

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: blog de Keith Barrington
Date: Friday, May 17, 2013 11:47:56 PM

more

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From: GONZALO LUIS MARIANI [mailto:gonzalo.mariani@hospitalitaliano.org.ar]
Sent: Friday, May 17, 2013 7:48 PM
To: Wally Carlo, M.D.
Subject: blog de Keith Barrington

Hola Wally, en estos dias descubri este blog, quizas lo conozcas, fijate el comentario de Keith on the SUPPORT issue (http://neonatalresearch.org/2013/05/14/support-even-better-than-originally-thought/)

Abrazo

Gonzalo

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: mas del blog de KB
Date: Friday, May 17, 2013 11:45:01 PM

Rose:

I had not seen these. You will enjoy them.

wally

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From: GONZALO LUIS MARIANI [mailto:gonzalo.mariani@hospitalitaliano.org.ar]
Sent: Friday, May 17, 2013 8:03 PM
To: Wally Carlo, M.D.
Subject: mas del blog de KB

Imperdibles:
http://neonatalresearch.org/2013/04/16/now-we-will-have-to-know-the-results-of-our-research-before-we-start-the-study/
http://neonatalresearch.org/2013/04/16/how-to-show-you-dont-understand-research-in-critical-patients/
http://neonatalresearch.org/2013/04/16/no-ethical-breakdown-here/
http://neonatalresearch.org/2013/04/20/even-more-supportive/
http://neonatalresearch.org/2013/04/25/more-support-for-support/

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 17, 2013 8:37 AM
To: Rowe, Mona (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: another editorial

http://www.neonatologyresearch.com/?page_id=3701

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Blansfield, Earl (NIH/NICHD) [E]

From: Kaeser, Lisa (NIH/NICHD) [E]
Sent: Friday, May 17, 2013 8:14 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: SUPPORT mention

Hi – thought you might be interested in the following exchange from Wednesday's Senate appropriations hearing, if you haven't already seen (I believe this was the only mention of any of NICHD's work, but am double checking):

Sen. SHELBY (ranking minority member, R-AL):

Thank you. First of all, I want to associate myself with the remarks of Senator Mikulski. I -- she said it so well. I believe that this committee in this Congress that the top investment we can make in America to save life, to improve lives, to (inaudible) the American people is to invest about here in NIH I believe this. I would -- I'd like to see us double. I know that's hard to do but, you know, at least get on the upward trend not the downward trend of biomedical research in this country.

And I'm saying that because I've seen the results of which Senator Mikulski has pointed out, Senator Harkin as and others, Senator Moran.

Having said that, Dr. Collins, I want to get a little parochial if I can and then I'll get back, researchers at the University of Alabama in Birmingham, as you well know, conducted an important study on very premature babies, a support study from 2004 to 2009 that was funded by the National Institute of Health. Researchers at more than 20 sites were trying to understand, as I understand it, the proper oxygen levels for these vulnerable premature babies by comparing two ranges of oxygen saturation within the standard of care at that time.

It's my understanding that the support study has had an important effect to clinical care. Dr. Collins I am (inaudible) this research like this that study and ultimately improve the standard of care.

COLLINS:

Well, Senator Shelby, thank you for the question, very important indeed. Standard of care reflects what we know at that time, and oftentimes, we don't know enough...

SHELBY:

Yes.

COLLINS:

... and so it may be a rather broad range of options and physicians and other caregivers who are trying to do the best job of taking care of patients and patients who are seeking the best care may not be well served by all the entire range of opportunities that are called standard of care. That was certainly the case for the study of the optimum oxygen levels to give to premature babies.

SHELBY:

But you learned by investigating and by studying, that's the bottom-line...

(CROSSTALK)

COLLINS:

Exaclty right. So, for us at NIH, we invest heavily in these kinds of studies. Let me give you another couple of examples. Individuals who are going through hemodialysis and there are a lot, sad to say, many of them because of diabetes. There has never really been a clear understanding of what the right schedule is for hemodialysis. How many times a week? How many hours? And that's a huge impact on somebody's quality of life in terms of how much time they are spending there, but also quality of life is dependent on how effective the dialysis is.

So, a study called Time that we have been funding, aimed to try to get an answer to that. All of the standard of care, everybody in that study is getting the kind of treatment that you would consider standard but we're trying t find the sweet spot to do a refinement of that.

SHELBY:

Sure.

COLLINS:

I could site you two or three others. This is very important and yet we depend upon patient...

(CROSSTALK)

SHELBY:

It goes to the basis of your research, does it not?

COLLINS:

Yes, it does. That's what our goal is, is to try to be sure that people get the best possible information in order to guide their medical care.

SHELBY:

As you -- as you well know, the UAB received a letter from the Office of Human Research Protections about the support clinical trial that we're carrying out under the auspices of NIH. And the OHRP determined that AUB should have informed parents of an increased risk death of their infant by participating in the study. But it was my understanding that the risk were unknown at the time of the study's commencement in 2004, and in there was no scientific -- specific scientific data that existed at the start of the study that shown in the increased risk.

Were babies in that study at any greater risk than babies not in the study? Do you know?

COLLINS:

No, senator. I don't believe they were.

Lisa Kaeser, J.D.
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Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 2:06 PM
To: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN DSMC

The DSMC has not yet seen the checklist. I have looked at the critical elements and we could (b)(5)

(b)(5)

I can give them access to the OHRP determination letter and the public citizen's documents.

If this is ok, we can move forward with our note to the DSMC.

Thanks for everyone's help.
Rose

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From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 1:13 PM
To: Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN DSMC

I agree with this approach, but would also add that (b)(5)

(b)(5) Have they seen it?

Yvonne T. Maddox, Ph.D.
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From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 11:26 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Re: NRN DSMC

Rose,
The DSMC could review the (b)(5)
(b)(5) It would be up to the DSMC members what those critical elements are.
Cathy

Catherine Y Spong MD
Spongc@mail.nih.gov
301 435 6894

On May 16, 2013, at 9:27 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> HI
> We have the NRN DSMC set up to meet on June 4 and Chris Gleason (Chair) had a few questions—I can summarize #1;
> For #2 – there is a link that the FDA uses from the CFR-
>
> http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25
>
> It would be good if have some guidelines for the DSMC. I do not think they should be (b)(5)
> (b)(5)
>
> (b)(5)
>
> *Chris*

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 12:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN DSMC

I don't know if the MFMU DSMC does, I think (b)(5)
(b)(5)
(b)(5) I think it is a reasonable way to do it.
Cathy

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 12:32 PM
To: Spong, Catherine (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN DSMC

If the MFMU DCC reviews the MFMU consent forms, we should (b)(5) – does the MFMU DSMC review individual consent forms?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 12:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN DSMC

(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 12:28 PM
To: Spong, Catherine (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: NRN DSMC

Cathy
We now have 44 hospitals in the NRN that recruit patients – this would mean 44 consents per year per study (we have 6 interventional trials ongoing currently). I think (b)(5)
(b)(5)

Rose
Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, May 16, 2013 11:26 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Re: NRN DSMC

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The DSMC could (b)(5)
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Cathy

Catherine Y Spong MD
Spongc@mail.nih.gov
301 435 6894

On May 16, 2013, at 9:27 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> HI
> We have the NRN DSMC set up to meet on June 4 and Chris Gleason (Chair) had a few questions—I can summarize #1;
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> (b)(5)

(b)(5)

Chris

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D.
To: William Tarnow-Mordi; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: draft letter to NEJM re Magnus and Caplan on parent partnership in research
Date: Thursday, May 16, 2013 2:40:25 AM

William.

I cannot open your attachment.

Wally

-----Original message-----

From: William Tarnow-Mordi <williamtm@med.usyd.edu.au>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, Neil Finer <nfiner@ucsd.edu>, Rosemary Higgins <higginsr@mail.nih.gov>
Sent: Thu, May 16, 2013 06:29:52 GMT+00:00
Subject: draft letter to NEJM re Magnus and Caplan on parent partnership in research

Dear Wally, Neil and Rose

I attach in confidence a draft letter to NEJM in response to the Perspective article by Magnus and Caplan on April 18, also attached. The letter is from myself as an individual, Melinda Cruz, Parent and CEO of Miracle Babies Foundation, Australia, and Kristine Brite McCormick, parent advocate for neonatal pulse oximetry screening to detect congenital heart disease, Indiana, whom I met at the Patient Safety Summit in California in January. Letters are limited to 175 words and 3 authors.

Your comments would be appreciated.

We emphasise in the Letter that no criticism is intended of SUPPORT or any of the oxygen targeting studies, which were designed before the recent US, UK and Australian government recommendations on patient participation were made.

We will also show this for information and comment to my BOOST II Australia co-investigators, Brian Darlow, our UK colleagues and Barbara Schmidt and Robin Whyte of COT.

best wishes

William

--
William Tarnow-Mordi
Professor of Neonatal Medicine, Westmead Hospital
NHMRC Clinical Trials Centre, University of Sydney,
Foundation Director
Westmead International Network for Neonatal Education and Research
WINNER Centre - working together to win healthy survival.

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 15, 2013 10:46 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Interesting tweet - he needs an editor!

Arthur Caplan
@ArthurCaplan

NIH Director Collins just took issue Senate Appropriations committee with OHRP criticism of neonatal SUPPORT study. Said no addition risk!

02:22 PM - 15 May 13

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

From: Mondoro, Traci (NIH/NHLBI) [E]
To: Willinger, Marian (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PLEASE READ: FW: NICHD NRN DSMC Review of Active NRN Trial Model Consents
Date: Wednesday, May 15, 2013 2:13:51 PM

I am on a call right now, but I will ask my network project manager this afternoon what checklist we use to see if we have a checklist that you guys could comment on.

From: Willinger, Marian (NIH/NICHD) [E]
Sent: Wednesday, May 15, 2013 2:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Mondoro, Traci (NIH/NHLBI) [E]
Subject: RE: PLEASE READ: FW: NICHD NRN DSMC Review of Active NRN Trial Model Consents

There is no specific guidance . They review it based on current knowledge in neonatology, what is in the protocol and human subject protection. One of the members is an ethicist. Since the leadership requested this review, I think we (b)(5)
(b)(5)
Marian

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 15, 2013 2:01 PM
To: Mondoro, Traci (NIH/NHLBI) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ: FW: NICHD NRN DSMC Review of Active NRN Trial Model Consents

Traci –
I have attached the charter – since this has not come up before, we do not have specific checklists or guidance (but likely may have some going forward).
Thanks for responding so quickly!
Rose

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Mondoro, Traci (NIH/NHLBI) [E]
Sent: Wednesday, May 15, 2013 1:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: RE: PLEASE READ: FW: NICHD NRN DSMC Review of Active NRN Trial Model Consents

Rose and Marian,
My first question is—does the DSMC receive any guidance from NICHD on what to look for in an informed consent template?

Second, does RTI have a checklist they use when they review the individual consents? I will ask the DCC of my network to see if they have something.

Thanks, Traci

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 15, 2013 1:53 PM
To: Mondoro, Traci (NIH/NHLBI) [E]; Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: PLEASE READ: FW: NICHD NRN DSMC Review of Active NRN Trial Model Consents

Traci and marian-
Comments- I want to get back to Kris and Chris Gleason in the morning. If the leadership should be involved, I am happy to forward.
Thanks for your help

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, May 15, 2013 12:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: PLEASE READ: FW: NICHD NRN DSMC Review of Active NRN Trial Model Consents

Hi Rose,

I received a response back from Dr. Gleason just a bit ago regarding review of the 6 active NRN trial consents. She prefers extending our DSMC meeting June 4th by 2 hours. She's also requested further information, detailed instruction and outlined a process. Can you please provide a summary of concerns and a clear idea of what the DSMC should be looking for on each consent form--what are the criteria for a "pass"?. I think we can use the template below if you, Marian and Traci Mondoro are fine with it or anyone else that wanted to approve before it went out to all.

"I would go with Option 2 (extend the June 4 conference call by potentially 2 hrs) with 3 caveats/requests:
1. To guide their review of the active trial consents, DSMC members should each get a brief summary--from Rose?-- of the concerns raised by OHRP, Public Citizen (whether real or perceived) regarding the SUPPORT trial consent forms. If we're going to discuss the active consents at our June 4 conference call, DSMC members should receive this summary ASAP 2. Ideally, there should be a review template for each DSMC member to fill out for each model consent form. The template should give these reviewers a clear idea of what they should be looking for on each form--what are the criteria for a "pass"?. And the template should be simple, quick and easy to fill out (e.g., consent meets criteria, does not meet criteria, discussion needed) and should be due to Kris one day prior

(June 3) 3. We should leave open the possibility of a follow-up face-to-face meeting in DC, or perhaps a teleconference if there are unresolved issues and/or significant concerns raised at our June 4 conference call. If a face-to-face meeting in DC is deemed necessary, this could just be with me or me and Bob--representing the DSMC--because it would be virtually impossible to get a DSMC quorum to DC on short notice, especially at the beginning of the summer.
Chris"

I would like to also send out an email **today** just requesting the time extension and that further information is forthcoming as follows (**please let me know if you are ok with this**)?

Dear all,

This request is on behalf of NICHD:

NICHD and NHLBI leadership have communicated regarding the NRN trials. In view of the recent attention to the NRN's SUPPORT trial, we are requesting that the DSMC review or re-review the current sample consents for the six (6) ongoing studies. We are asking that this review to be conducted as part of the June 4th meeting and therefore we are extending the meeting to three (3) hours in light of other previously scheduled materials to reviews.

Further instruction and details on this process are forthcoming.

Please let me know if you have any conflict with our upcoming meeting being scheduled for ***June 4, 2013 from 11:00am to 2:00PM EST.*** *Please also note we will also ask Drs. Mondoro and Manno (NHLBI) to be present during the TOP consent review discussion.*

Thanks,
Kris

From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Safe Oxygen Targets for Preemies Unclear, Doctors to Choose May 10 13.pdf
Date: Monday, May 13, 2013 2:52:55 PM
Attachments: Safe Oxygen Targets for Preemies Unclear, Doctors to Choose May 10 13.pdf

Hi Rose, you probably saw this already, but if not.....

Carol

www.medscape.com

Safe Oxygen Targets for Preemies Unclear, Doctors to Choose

Neil Canavan | May 10, 2013

WASHINGTON, DC — Are lower oxygen saturation targets safe for extremely preterm infants? Two major new studies come to different conclusions.

"For years, we clinicians have searched for the right balance between the competing risks caused by oxygen excess and oxygen deprivation," said Barbara Schmidt, MD, chair in neonatology at the University of Pennsylvania in Philadelphia.

Dr. Schmidt presented 18-month outcomes from the Canadian Oxygen Trial here at the Pediatric Academic Societies 2013 Annual Meeting. The results were published online May 5 in *JAMA* to coincide with the presentation.

"We performed this double-blind randomized trial to help resolve the uncertainty," she explained.

In the Canadian trial, 2 levels of oxygen supplementation — target oxygen saturation measured by pulse oximetry of 85% to 89% and of 91% to 95% — started within 24 hours of birth, were compared in preterm infants born at 23 to 27 weeks. Treatment was to continue until the postmenstrual age of 40 weeks or hospital discharge.

The primary end point was the composite of infant death, survival with severe disability (such as bilateral blindness), and gross motor function impairment.

A total of 1201 infants were randomized in a 1:1 fashion to the higher or lower saturation target. To blind investigators to the treatment group, oximeters displayed saturation levels either 3% higher or 3% lower than the actual measures. Researchers adjusted the fraction of inspired oxygen to achieve a displayed saturation of 88% to 92%; to ensure overall safety, alarms were set at 86% and 94%.

At baseline, both groups were balanced for weight and sex ratio, singleton births, and exposure to antenatal corticosteroids.

For years, we clinicians have searched for the right balance between the competing risks caused by oxygen excess and oxygen deprivation.

Of note, the software for the oximeter was upgraded during the investigation. When measurements taken using old and new oximeter software were compared, the statistical differences were consistent.

After 18 months, there was no statistical difference between the lower and higher saturation groups in death or disability (51.5% vs 49.7%; $P = .52$).

In fact, "we found little evidence for differences in any of the components that make up the composite end point," Dr. Schmidt reported.

"Targeting the lower saturation range did reduce postmenstrual age at last use of oxygen therapy by almost 1 week ($P = .03$), but no other significant differences were seen in secondary outcomes, such as severe retinopathy or brain injury as seen on cranial ultrasound," she added.

After her presentation, Dr. Schmidt was asked by an audience member to consider her results in the light of the similar SUPPORT trial, which found greater mortality at lower saturation targets.

Dr. Schmidt replied that, although the trials do have similarities, there are also critical differences, particularly in the very highest and very lowest values actually observed for the 2 target ranges. It is possible that "we did not find excess mortality in the low target or increased retinopathy in the high target because of tighter control."

In practice, for levels outside the target range, "we believe that these alarm limits are critically important and need to be enforced at all times. We know it's difficult, but it needs to be done," she emphasized.

Results from a second study, known as the Benefits of Oxygen Saturation Targeting (BOOST II) trial, conflict with the findings of this Canadian study.

BOOST II Trial Halted

In the BOOST II trial, mortality differences between the 2 groups are significant, reported Benjamin Stenson, MD, from the Royal Infirmary of Edinburgh, in the United Kingdom, who presented the results here.

In fact, recruitment to the British and Australian BOOST II cohorts was stopped in December 2010 after an interim analysis of data showed an increased mortality risk in infants randomized to the lower saturation target.

The results were published online May 5 in the *New England Journal of Medicine* to coincide with their presentation.

When we revised oximeters, we saw a large and highly statistically difference in mortality.

The 5230 infants enrolled in the BOOST II trial were randomized in the 24 hours after birth to the same saturation target levels as the Canadian trial. As in the that study, oximeters were offset and investigators were blinded. Alarm limits for the oximeters varied by study site: in Australia, they were set at 86% and 94% (n = 1135); in New Zealand, they were set at 87% and 93% (n = 340); and in the United Kingdom, they were set at 94% and unit preference (n = 1350).

As in the Canadian trial, oximeters were upgraded midstudy, except in New Zealand, where the study had already been completed.

"When we were using the original oximeters, we saw no statistically significant differences in mortality between treatment groups," said Dr. Stenson. "However, when we revised oximeters, we saw a large and highly statistically difference in mortality." Survival was greater in infants in the higher saturation group than in the lower saturation group (23.1% vs 15.9%; risk ratio, 1.45; $P = .002$).

Table. BOOST II Mortality Outcomes By Oximeter Calibration

Software	85%–89% Saturation Target	91%–95% Saturation Target	Risk Ratio (95% Confidence Interval)
Old	15.6%	17.3%	0.90 (0.70–1.16)
New	23.2%	15.8%	1.47 (1.16–1.86)

Other differences were observed for secondary outcomes. There was less retinopathy in the lower group than in the higher group (10.6% vs 13.5%; $P = .045$), but more necrotizing enterocolitis (10.4% vs 8.0%; $P = .04$).

"Slightly more infants in the high-target group were oxygen-dependent at 36 weeks (RR, 0.88), but this was not observed in the British cohort," Dr. Stenson noted.

In an interview with *Medscape Medical News*, Lawrence Rhein, MD, director of the Center for Healthy Infant Lung Development at the Children's Hospital in Boston, Massachusetts, noted that "the take-home message of these studies is that close attention to the saturation limits is important."

He pointed out that the Canadian trial shows that paying close attention to the saturation targets results in no difference in outcome; there were no negative consequences in either treatment group.

Close attention to the saturation limits is important.

"But I think there's a huge asterisk in that," Dr. Rhein said. "No negative consequences with this practice assumes that people have paid, and will continue to pay, close attention to those saturation limits. Yet, in real-world practice, I'm not sure that always happens. So if you are going to practice that way, you have to make sure that you adhere very strictly within that low range."

Dr. Rhein pointed to a number of outliers in the BOOST trial — data points outside the target ranges where real dangers to the patients reside. "It was that issue that people were talking about, these excursions, and how you can avoid the greatest risk to patients at extremes of both ranges." Some hypothesize that these outliers explain the difference between the opposing findings of the 2 trials, Dr. Rhein said. If that is the case, that would tend to frame the controversy as one more of accuracy than of appropriate targeting.

"I would say that if you are going to change practice, err on the side of raising your lower target saturation limit, and then make sure that on the high end, you have the nurses maintain strict alarm limits," he said.

Raise the Lower Saturation Target

As for the protocols used in his unit, "our set points are 88% to 92%," Dr. Rhein said. "That way, when we do a good job of keeping within range, we won't have too many outliers that are less than 85%, like in the SUPPORT trial, and we shouldn't have too many that are above 95%." But again, this very much depends on the diligence of the staff.

Now that these much-anticipated data have been released, Dr. Rhein suggests that the next hot topic in neonatology is going to be long-term outcomes. "When big studies like this come out with preliminary findings, these short-term outcomes, the next thing people look for is what are these kids going to be like when they're 5."

Dr. Rhein said he would also like to see data on how long a given range of saturation targets should be sustained. "In all of these studies, they had a target range that stayed the same on day-of-life 1 and discharge. There are many units, including ours, that change the saturation parameters once a child reaches a gestational age of 33 to 36 weeks. That aspect wasn't addressed in these studies."

Dr. Schmidt, Dr. Stenson, and Dr. Rhein have disclosed no relevant financial relationships.

JAMA. Published online May 5, 2013. Abstract

N Engl J Med. Published online May 5, 2013. Abstract

Pediatric Academic Societies (PAS) 2013 Annual Meeting: Abstracts 2180.6 and 2180.8. Presented May 5, 2013.

Send comments and news tips to news@medscape.net.

Cite this article: Safe Oxygen Targets for Preemies Unclear, Doctors to Choose. *Medscape*. May 10, 2013.

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Wednesday, May 15, 2013 1:17 PM
To: 'Sidney Wolfe'
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: RE: Concerning the increasing efforts by NIH-funded researchers and others to fault the messengers (OHRP and ourselves---including internationally known bioethicist Ruth Macklin) instead of the addressing the message (unethical research)

Drs. Wolfe and Carome –

Although (or even because) I disagree with much of the premise below, I - along with Kathy Hudson, the NIH Deputy Director for Science, Outreach, and Policy - would be happy to meet with you to discuss the SUPPORT study. Whom should we contact to identify 45 minutes that would work for all of us?

Best, Alan

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

From: Sidney Wolfe [mailto:swolfe@citizen.org]
Sent: Friday, May 10, 2013 12:38 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Concerning the increasing efforts by NIH-funded researchers and others to fault the messengers (OHRP and ourselves---including internationally known bioethicist Ruth Macklin) instead of the addressing the message (unethical research)

Ruth Macklin, Ph.D., who co-authored our report, sent to both of you this week, has credentials that include an important NIH connection:

> **Professor (Bioethics) in the Department of Epidemiology & Population Health at Albert Einstein College of Medicine in Bronx, NY**
>
> **Director, Training Program in Research Ethics in the Americas, sponsored by the NIH Fogarty International Center.**
>
> **Member of Board of Directors and Past President of the International Association of Bioethics.**

In the short and long run, failing to focus on and to remedy the processes whereby NIH, the SUPPORT study researchers, the IRBs and others have signed off on such inadequate consent forms will cause much more damage than the public airing of the problems themselves. It has been our intention and, we are certain, that of the OHRP to prevent such future occurrences. We hope you and your colleagues understand this and act accordingly.

We would be glad to meet with you to discuss these issues further.

Sidney M. Wolfe MD, Michael Carome, MD
Health Research Group at Public Citizen

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 14, 2013 10:30 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Suggested correction to OHRP-UAB draft letter

Okey dokey. (b)(5) I am going to turn to other things..... and not respond....

-----Original Message-----
From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, May 14, 2013 10:27 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH)
Subject: Re: Suggested correction to OHRP-UAB draft letter

Kathy,

We had thought that NIH might prefer that the (b)(5)
(b)(5)

That shouldn't (b)(5)
(b)(5) we could certainly do that.

Best,
Jerry

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Tuesday, May 14, 2013 10:03 PM
To: Menikoff, Jerry (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH)
Subject: RE: Suggested correction to OHRP-UAB draft letter

Thanks for letting us know Jerry.

Just so you know, the NZ consent is not alone in its language. None of the four sister studies state that either experimental arm had an increased risk of mortality. The four sister studies have remarkably similar language. As an outsider, I (b)(5) by the first lines of the NZ and Canadian consents (maybe others) that say to the parents, "thank you for taking time to even think about this at really awful and painful time for you and your family." (paraphrasing....)

On the issue of citing the NZ consent, does OHRP generally weigh in on consent forms of institutions that are not subject to its' oversight? I can see that might (b)(5)
(b)(5)

OHRP needs to c (b)(5)
(b)(5)

Happy to discuss.

Best,
Kathy

-----Original Message-----
From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, May 14, 2013 9:20 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH)
Subject: RE: Suggested correction to OHRP-UAB draft letter

Kathy,

Thanks again for pointing out the information about the New Zealand consent form to us. We still think (b)(5)
(b)(5) But we propose to make several changes to the footnote, i (b)(5)
(b)(5)

Thus, after these changes, footnote 2 would read as indicated below.

Best,
Jerry

Here is what the revised footnote 2 would say:

(b)(5)

Blansfield, Earl (NIH/NICHD) [E]

From: Houser, Anne (NIH/OD) [E]
Sent: Tuesday, May 14, 2013 1:39 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Cc: White, Pat (NIH/OD) [E]; Houser, Anne (NIH/OD) [E]
Subject: Dr. Hudson asked me to send you

These two questions, which we expect to have asked of Dr. Collins at the hearing tomorrow. This is also why she was trying to reach you.

SUPPORT Study

(b)(5)

Anne S. Houser
Office of Legislative Policy and Analysis
National Institutes of Health
Building 1, Room 244
1 Center Drive, MSC 0160
Bethesda, MD 20892-0160
Phone: (301) 496-3471
Fax: (301) 496-0840
email: Housera@od.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, May 14, 2013 12:41 PM
To: Alan Fleischman
Subject: RE: Thoughts about SUPPORT

Thanks, Alan. You will be glad to know that such a symposium is in the works already.

Best, Alan

From: Alan Fleischman [mailto:arf@fleischman.net]
Sent: Tuesday, May 14, 2013 9:17 AM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Thoughts about SUPPORT

Alan,

I hope this email finds you well. I have been thinking a lot about the recent kertuffle concerning the SUPPORT study in the Neonatal Network. I had no role in the study or its review. While I believe OHRP was heavy handed and missed an opportunity to be helpful rather than punitive, I do believe the informed consent was not "optimal." I think the crux of the problem is sorting out how to write informed consents for research with diseases or disorders that have death and disability as likely outcomes. About eight years ago, I catalyzed a significant change in how the Children's Oncology Group does its consents, separating the clinical issues about the disease and its treatment from the research questions and the research risks.

I think this is particularly important in comparative effectiveness research when "standard" treatments are being compared. Just because the two arms are standard does not mean that there are no risks of randomization itself and of "protocolization" instead of individualized care. But the inherent risks of the disease need to be separated from the risks of the research. I believe it is easy to describe these issues in consent forms and not discourage participation.

I would be happy to discuss these issues further. I suggest you consider a national symposium to discuss informed consent issues as a response to the OHRP criticism. You do not need to accept "guilt" in order to want to enhance the research consent process among NICHD funded children's research studies.

By chance, I am on my way to Bethesda for a NIAID DSMB, arriving this afternoon with meetings on Wednesday and Thursday. I would be happy to meet in person if you are available and interested, today anytime after 4PM or tomorrow anytime after 5:30PM. Alternatively, I am happy to chat next week or in the future if you think I can be of help.

Alan

Alan R. Fleischman, M. D.
arf@fleischman.net
917 439-6364

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: REquest for GDB, SUPPORT and FU forms
Date: Tuesday, May 14, 2013 8:08:44 AM

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Pablo Sanchez [mailto:Pablo.Sanchez@UTSouthwestern.edu]
Sent: Monday, May 13, 2013 07:22 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

Yes--pablo

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Monday, May 13, 2013 9:06 AM
To: (suhas.kallapur@cchmc.org); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); dstevenson@stanford.edu; Haresh Kirpalani (KIRPALANIH@email.chop.edu); Krisa Van Meurs (vanmeurs@stanford.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion; mcw3@po.cwru.edu; Pablo Sanchez; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD)
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

Please send in your vote for the request below.

Stephanie Wilson Archer
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 02, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha

Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: REquest for GDB, SUPPORT and FU forms

Hi-

Jack Sinclair is interested in exploring use of the SUPPORT database to develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD.
See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.
Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D.
To: Shankaran, Seetha; Higgins, Rosemary (NIH/NICHD) [E]; Neil
Subject: RE: A SUPPORT question
Date: Monday, May 13, 2013 1:17:59 PM

Hi Seetha, Neil, and Rose:

The causes of death were published in the O2 sat paper appendix. A statement on the paper states that they did not differ between groups.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, May 13, 2013 9:53 AM
To: Rose; Wally Carlo, M.D.; Neil
Subject: Fwd: A SUPPORT question

Rose, Wally , Neil
What shall I say----pl advise
Seetha

Sent from my iPhone

Begin forwarded message:

> **From:** "Shankaran, Seetha" <sshankar@med.wayne.edu>
> **Date:** May 13, 2013 10:51:14 AM EDT
> **To:** "Barks, John" <jbarks@med.umich.edu>
> **Subject: Re: A SUPPORT question**
>
> John
> Let me check and get back to you
> Seetha
>
> Sent from my iPhone

On May 13, 2013, at 9:28 AM, "Barks, John" <jbarks@med.umich.edu> wrote:

Seetha: Folks here keep asking me: Does the NRN have data on causes of death in SUPPORT, i.e. what disease process, if any in particular, was responsible for the increase in death in the lower target group? Is there a secondary analysis paper in the works on that question?
Thanks
John

****

Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues

From: Finer, Neil
To: Shankaran, Seetha; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: RE: A SUPPORT question
Date: Monday, May 13, 2013 10:54:57 AM

Wally has looked at this closer than anyone else-To my knowledge we have not identified a single mechanism of death or disease state that was different between the groups
Wally, I bow to your knowledge
Neil

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Monday, May 13, 2013 4:53 PM
To: Rose; Wally Carlo, M.D.; Finer, Neil
Subject: Fwd: A SUPPORT question

Rose, Wally , Neil
What shall I say----pl advise
Seetha

Sent from my iPhone

Begin forwarded message:

> **From:** "Shankaran, Seetha" <sshankar@med.wayne.edu>
> **Date:** May 13, 2013 10:51:14 AM EDT
> **To:** "Barks, John" <jbarks@med.umich.edu>
> **Subject: Re: A SUPPORT question**
>
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> > Thanks
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> >
> > **********
> >
> > Electronic Mail is not secure, may not be read every day, and should not be used for urgent or sensitive issues

From: Walsh, Michele
To: Archer, Stephanie (NIH/NICHD) [E]; suhas.kallapur@cchmc.org; AnnaMaria.hibbs@cwru.edu; dstevenson@stanford.edu; KIRPALANIH@email.chop.edu; vanmeurs@stanford.edu; kurt.schibler@cchmc.org; luc.brion@utsouthwestern.edu; mcw3@po.cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; Schmidt, Barbara (Neonatology); Seetha Shankaran ; bsood@med.wayne.edu; Truog, William (MD)
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms
Date: Monday, May 13, 2013 10:34:49 AM

yes

-----Original Message-----
From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Mon 5/13/2013 10:05 AM
To: (suhas.kallapur@cchmc.org); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); dstevenson@stanford.edu; Haresh Kirpalani (KIRPALANIH@email.chop.edu); Krisa Van Meurs (vanmeurs@stanford.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); mcw3@po.cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD)
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Tel. 301-496-0430
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Thanks
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Rosemary D. Higgins, MD
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higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: letter to OHRP
Date: Monday, May 13, 2013 8:36:51 AM

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Collins, Francis (NIH/OD) [E]
Sent: Saturday, May 11, 2013 01:32 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: letter to OHRP

Yes, I would think (b)(5)
(b)(5)

FC

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 8:11 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: letter to OHRP

Interesting hhs never shared this letter with us.... Should we (b)(5)
(b)(5)
Thoughts?

-----Original Message-----
From: Lantos, John [mailto:jlantos@cmh.edu]
Sent: Friday, May 10, 2013 5:43 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: letter to OHRP

Kathy,

And here is a letter I sent to OHRP, with a copy to Secretary Sibelius. I haven't heard back.

J
John D. Lantos M.D.
816-701-5284

Are you interested in an on-line certificate program in Pediatric Bioethics?
Visit the the CMH Bioethics Center web page: http://www.childrensmercy.org/cmbc.
We have a few spots left for 2013-14.

From: Lantos, John
Sent: Friday, April 19, 2013 13:13
To: 'jerry.menikoff@hhs.gov'; 'lisa.buchanan@hhs.gov'
Cc: 'Kathleen.Sebelius@hhs.gov'

Subject: Please apologize and correct your misrepresentations

April 19, 2013,

Dear Drs. Menikoff and Buchanan,

I think that you have an obligation to the parents of babies who were in the SUPPORT study, and to the parents of babies who might be enrolled in future studies, to clarify to the public, in a press release, that there was no harm done to babies who were in the SUPPORT study. I think that you should also publically repudiate Public Citizen for the use that they have made of your letter to UAB and the implication that not only the SUPPORT study but all studies of the NICHD neonatal network should be halted. Letting your letter to UAB stand as written in the public record has the potential to harm many babies by leading their parents to the misleading judgment that research is riskier than it is.

In particular, you write:

"It would have been appropriate for the consent form to explain (i) that the study involves substantial risks, and that there is significant evidence from past research indicating that the level of oxygen provided to an infant can have an important effect on many outcomes, including whether the infant becomes blind, develops serious brain injury, and even possibly whether the infant dies; (ii) that by participating in this study, the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received, though it is not possible to predict what that change will be; (iii) that some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind; and (iv) that the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death."

Number (ii) is true. Numbers (i), (iii) and (iv) are not. The study did not involve substantial risks compared to the alternative – that is, oxygen levels determined based on clinical judgment. The investigators didn't believe this to be true when the study was designed. And they were right. The results from the study showed that it wasn't true. You should acknowledge that. The infants in the higher oxygen group did not have a greater risk of going blind, compared to either conventional therapy or, as it turned out, compared to the lower oxygen group. (They had higher rates of retinopathy, but rates of blindness were not different.) You should acknowledge that. The level of oxygen was not thought to increase the risk of brain injury or death compared to conventional therapy or in a comparison of the two arms of the trial. And it didn't.

The Editors of the New England Journal of Medicine (http://www.nejm.org/doi/full/10.1056/NEJMe1304996?query=featured_home)
and the investigators (http://www.nejm.org/doi/full/10.1056/NEJMc1304827?query=featured_home) vigorously dispute your interpretations of the study and the results. http://www.nejm.org/doi/full/10.1056/NEJMe1304996?query=featured_home

Allowing your misleading statements to stand, in the public record, will mislead parents, lead them to decide not to participate in NICHD trials, which might be worse for the babies and worse for future babies. You owe it to the doctors, and to America's children to apologize for and correct these statements. Please do the right thing.

John Lantos M.D.

John Lantos M.D.

Director, Children's Mercy Bioethics Center

Children's Mercy Hospital

2401 Gilham Rd.

Kansas City, MO 64108

816-701-5283 (phone)

816-701-5286 (fax)

jlantos@cmh.edu<mailto:jlantos@cmh.edu>

Assistant: Mary Ellen Hudson, 816-701-5284

Visit the Children's Mercy Bioethics Center web page<http://www.cmh.edu/cmbc> (http://www.childrensmercy.org/cmbc) for general information and a link to the application for the 2013-2014 CMBC Certificate Program in Pediatric Bioethics. The deadline for applications is Friday, March 1st! We will consider applications as they are received.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: bizarre language
Date: Monday, May 13, 2013 8:36:27 AM
Attachments: BOOST-NZ information_consent[1].pdf

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 11:37 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: bizarre language

I clearly need a vacation as I have turned into something bordering on an ocd attorney....

Here is my current obsession.

1. In the latest version of the ohrp letter to uab, (b)(5)

(b)(5)

2. This footnote (b)(5)

(b)(5)

(b)(5)

4. Thus, I think (b)(5)

(b)(5)

Thoughts?

<<BOOST-NZ information_consent[1].pdf>>

UNIVERSITY OF OTAGO

Te Whare Wānanga o Otāgo

CHRISTCHURCH WOMEN'S

INFORMATION SHEET

What oxygen saturation level should we target in very preterm infants? – a randomised controlled trial (RCT). The BOOST (Benefits Of Oxygen Saturation Targeting) – NZ study.

Thank you for taking time to read this when so much is happening to your baby. We know it is a difficult time for you. We would like to invite you and your baby to take part in the BOOST - NZ study.

Summary

- **You may either be at risk of delivering more than 12 weeks early; or Your baby has already been born less than 28 weeks gestation and is less than one day old**
- **Very premature babies need treatment with oxygen because their lungs are not fully developed**
- **We want to understand whether it's better for a baby's long term health to aim to keep the blood oxygen level at either 85-89% or 91-95% saturation.**

Background to the study

Modern intensive care now enables many very preterm babies to survive who otherwise may not do so. One of the most important aspects of this care is help with breathing and treatment with oxygen because the baby's lungs are very immature. It is important to monitor the blood oxygen level (oxygen saturation) to try to make sure they do not have either too much or too little.

Too high oxygen in the blood for long periods may

- contribute to abnormal development of the retina (a condition called retinopathy of prematurity – ROP) and affect vision – it even is possible for some babies with ROP to become blind
- contribute to changes in the lungs that mean the baby needs ongoing help with breathing for weeks or months (a condition called bronchopulmonary dysplasia - BPD)
- be one cause of damage to brain cells and lead to developmental problems

Too low oxygen in the blood for long periods may

- increase the risk the baby will not survive or contribute to poor growth
- raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia
- damage the brain cells and lead to developmental problems

Blood oxygen changes every few seconds and cannot be controlled exactly. But most doctors who care for very preterm babies around the world target an oxygen saturation between 85% and 95%. But this range is based upon opinion and exactly what is the optimal range is unknown.

What is the purpose of the study?

The aim of this study is to determine, *within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%)*, whether targeting the lower end of this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability.

This is the New Zealand arm of an international study that will involve 5,000 very preterm infants in Australia, the United Kingdom, Scandinavia, Germany, Spain, Canada, and the United States.
In this country the study has been funded by the New Zealand Health Research Council

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Department of Paediatrics
2 Riccarton Avenue, PO Box 4345, Christchurch, New Zealand.
Tel 64 3 364 0747 • Fax 64 3 364 0747 • Email *paediatrics@chmeds.ac.nz*
www.chmeds.ac.nz
DUNEDIN • CHRISTCHURCH • WELLINGTON • AUCKLAND

WHAT THE RESEARCH INVOLVES FOR YOU OR YOUR CHILD

Babies are eligible for the study if they are

- born at less than 28 completed weeks
- and are less than 24 hours old when the study starts

All very preterm babies, whether in this study or not, have their blood oxygen saturation monitored continuously. The monitor we use for this is called an "oximeter" and it works via a small probe attached to the hand or the foot. The probe shines a light through the tissues and from the return signal the oxygen saturation of the blood can be measured.

This picture shows an oxygen sensor which has been placed on the baby's foot and covered to keep out the light. The sensor lead is connected to the oximeter, which is not shown.

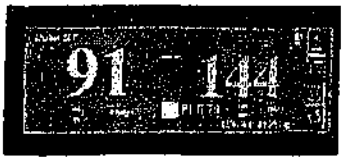
For all babies who need supplementary oxygen the doctors and nurses will aim for a displayed target range of 88%-92%. If you agree to your baby joining the study, the only difference will be that your baby will be allocated a study oximeter at random (like tossing a coin), which has been altered to read either slightly higher or slightly lower than the actual saturation.

- One type reads 88% - 92% when the oxygen saturation is actually 3% lower at 85% - 89%
- The other type reads 88% - 92% when the saturation is actually 3% higher at 91% - 95%

The doctors and nurses will aim for an oxygen saturation of 88% - 92%, with both types of oximeter.

- Neither you nor the doctors or nurses can choose or know which type of oximeter your baby gets
- Above and below the range of 85%-95% each oximeter will always show the true oxygen saturation
- For babies who do not need extra oxygen, the study oximeter will often read up to 100%. That is quite normal
- All babies (whether in the study or not) will need occasional blood tests as part of routine care to check other things such as carbon dioxide

The pulse oximeter is a machine about the same size as a DVD player. It is kept on a shelf near the baby. This picture shows a display from a pulse oximeter. The baby's oxygen saturation reading is 91% and heart rate is 144.



- Information will also be collected on your baby's antenatal and neonatal course and kept in a confidential way using code numbers. No reports from the study will identify you or your baby in any way.
- It's very important that we find out how your baby is doing at 2 years of age. When you go home, we'd like to keep in touch, so we will record your contact details. It's important to tell us if they change.
- When your baby is 2 years old (corrected for prematurity) he/she will be invited to be assessed by a paediatrician and have a formal test of development (the Bayley Test) and of vision.
- Most children will still be in routine paediatric follow-up at this time so the paediatric assessment will be at the time of a normal out-patient visit. The Bayley Test and vision assessment may require one or two extra visits and take 45 minutes and 30 minutes each.

DESCRIPTION OF INCONVENIENCES OR HAZARDS WHICH MIGHT BE EXPECTED:
We do not expect any difficulties at all with this study for your baby.

- Too much or too little blood oxygen might affect long term health and development. These risks exist whether or not your baby is in the study.
- The main benefit is to help improve the care of future very premature babies.
- As noted the Bayley Test and vision assessment might require two extra visits. We can help with the expense of this, for example by providing a petrol voucher, if necessary

Participation:
Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part your baby will receive the usual care. If you do agree to take part you are free to withdraw your baby from this study at any time, without having to give a reason, and this will in no way affect your baby's care.

Compensation:
In the unlikely event of a physical injury as a result of your participation in this study, you will be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually only provides partial reimbursement of costs and expenses and there may be no lump sum compensation. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

Ethical approval:
This study has been approved by the Multi-Region Ethics Committee, which reviews national and multiregional studies.

IF YOU WANT TO KNOW MORE:
If you want to know anything further about this study (either now or at any later date) please feel free to ask.

Prof Brian Darlow	Principal investigator BOOST-NZ Paediatrician, Christchurch Women's Neonatal Unit Phone: 3644-699 : carries pager
Dr Glynn Russell	Paediatrician, Christchurch Women's Neonatal Unit Phone: 3644-699 : carries pager
Nicki McNeill/Trish Graham	Research Nurses BOOST-NZ Christchurch Women's Neonatal Unit Phone: 3644-742: has answerphone

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate: phone 3777 501
Or free phone if residing out of town: 0800 377 766

UNIVERSITY OF OTAGO

Te Whare Wānanga o Otāgo

CHRISTCHURCH WOMEN'S

CONSENT FORM

PROJECT TITLE: What oxygen saturation level should we target in very preterm infants? – a randomised controlled trial (RCT). The BOOST-NZ study

INVESTIGATORS: Professor Brian Darlow, Department of Paediatrics, Christchurch School of Medicine and Health Sciences.
Dr Carl Kuschel, National Women's Health, Auckland City Hospital
Dr Michael Meyer, Middlemore Hospital
Dr Michael Hewson, Wellington Hospital
Dr Roland Broadbent, Dunedin Hospital
Dr Cynthia Cole, Harvard University, Boston

VENUE: Christchurch Women's Hospital, Christchurch; National Women's Health, Auckland; Middlemore Hospital; Wellington Women's Hospital; Dunedin Hospital

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STATEMENT BY PARENT:
I/we have read and understood the attached information sheets and have had the opportunity for discussion with a doctor. I/we am/are satisfied with answers I/we have been given. I/we understand that taking part in this study is voluntary (my/our choice) and that I/we may withdraw my baby from this study at any time, and this will in no way affect my baby's or my family's continuing or future health care in any way.

I/we understand that participation in this study is confidential and that no material which could identify me/us, or my/our child, will be used in any reports on this study.

I/we understand the compensation provisions for this study.
I/we have had time to consider whether to take part.
I/we know whom to contact if I have any questions about the study.
I/we wish to receive a summary of the results of the research. **Yes / No**

I/we give consent for my midwife / GP to be notified of my baby's participation in this research. **Yes / No**

I consent to my baby _____(baby's name) taking part in this study.

Signed:----------Print---------- Date: / /

----------Print---------- Date: / /

Doctor:----------Print---------- Date: / /

Christchurch School of Medicine & Health Sciences
Department of Paediatrics
2 Riccarton Avenue, PO Box 4345, Christchurch, New Zealand.
Tel 64 3 364 0747 • Fax 64 3 364 0747 • Email paediatrics@chmeds.ac.nz
www.chmeds.ac.nz

Request for Interpreter

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
	Other languages to be added following consultation with relevant communities.		

2001 Census question about ethnicity:

Which ethnic group do you belong to?
Mark the space or spaces which apply to you.

- NZ European
- Māori
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese
- Indian
- other (such as *DUTCH, JAPANESE, TOKELAUAN). Please state:*

Ko tēhea momo tāngata e whai pānga atu ana koe?
Tohua te katoa o raro nei e hāngai ana ki a koe.

- Pākehā
- Māori
- Hāmoa
- Māori Kuki Airani
- Tonga
- Niue
- Hainamana
- Inia
- tētahi atu (pērā i *TATIMANA, HAPANĪHI, TOKELAU). Tuhia mai:*

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: BOOST II NZ
Date: Monday, May 13, 2013 8:36:02 AM
Attachments: BOOST NZ PI Form-Final-Chch.doc

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Brian Darlow [mailto:brian.darlow@otago.ac.nz]
Sent: Saturday, May 11, 2013 04:44 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: RE: BOOST II NZ

Dear Rose, Thanks. Yes, good to see you at PAS. An interesting meeting!.
My apologies, I thought our PIS and consent form had gone to all NeOPRoM members. It as attached - each site had their own institutional heading.

Thanks for sending the updated AAP recommemdations - the section on Sat targets is very sensible and clearly written. Very helpful.

Kindest regards

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Sunday, 12 May 2013 2:57 a.m.
To: Brian Darlow
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: BOOST II NZ

Hi Brian -
Nice to see you at PAS.
Would you mind sharing the BOOST II NZ sample consent with us at NIH?
Thanks in advance for your help.
With best regards,
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

INFORMATION SHEET

What oxygen saturation level should we target in very preterm infants? – a randomised controlled trial (RCT). The BOOST (Benefits Of Oxygen Saturation Targeting) – NZ study.

Thank you for taking time to read this when so much is happening to your baby. We know it is a difficult time for you. We would like to invite you and your baby to take part in the BOOST - NZ study.

Summary

- **You may either be at risk of delivering more than 12 weeks early; or Your baby has already been born less than 28 weeks gestation and is less than one day old**
- **Very premature babies need treatment with oxygen because their lungs are not fully developed**
- **We want to understand whether it's better for a baby's long term health to aim to keep the blood oxygen level at either 85-89% or 91-95% saturation.**

Background to the study

Modern intensive care now enables many very preterm babies to survive who otherwise may not do so. One of the most important aspects of this care is help with breathing and treatment with oxygen because the baby's lungs are very immature. It is important to monitor the blood oxygen level (oxygen saturation) to try to make sure they do not have either too much or too little.

Too high oxygen in the blood for long periods may

- contribute to abnormal development of the retina (a condition called retinopathy of prematurity – ROP) and affect vision – it even is possible for some babies with ROP to become blind
- contribute to changes in the lungs that mean the baby needs ongoing help with breathing for weeks or months (a condition called bronchopulmonary dysplasia - BPD)
- be one cause of damage to brain cells and lead to developmental problems

Too low oxygen in the blood for long periods may

- increase the risk the baby will not survive or contribute to poor growth
- raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia
- damage the brain cells and lead to developmental problems

Blood oxygen changes every few seconds and cannot be controlled exactly. But most doctors who care for very preterm babies around the world target an oxygen saturation between 85% and 95%. But this range is based upon opinion and exactly what is the optimal range is unknown.

What is the purpose of the study?

The aim of this study is to determine, *within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%)*, whether targeting the lower end of this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability.

This is the New Zealand arm of an international study that will involve 5,000 very preterm infants in Australia, the United Kingdom, Scandinavia, Germany, Spain, Canada, and the United States.
In this country the study has been funded by the New Zealand Health Research Council

WHAT THE RESEARCH INVOLVES FOR YOU OR YOUR CHILD

Babies are eligible for the study if they are

- born at less than 28 completed weeks
- and are less than 24 hours old when the study starts

All very preterm babies, whether in this study or not, have their blood oxygen saturation monitored continuously. The monitor we use for this is called an "oximeter" and it works via a small probe attached to the hand or the foot. The probe shines a light through the tissues and from the return signal the oxygen saturation of the blood can be measured.

This picture shows an oxygen sensor, which has been placed on the baby's foot and covered to keep out the light. The sensor lead is connected to an oximeter, which is not shown.

For all babies who need supplementary oxygen the doctors and nurses will aim for a displayed target range of 88%-92%. If you agree to your baby joining the study, the only difference will be that your baby will be allocated a study oximeter at random (like tossing a coin), which has been altered to read either slightly higher or slightly lower than the actual saturation.

- One type reads 88% - 92% when the oxygen saturation is actually 3% lower at 85% - 89%.
- The other type reads 88% - 92% when the saturation is actually 3% higher at 91% - 95%.

The doctors and nurses will aim for an oxygen saturation of 88% - 92%, with both types of oximeter.

- Neither you nor the doctors or nurses can choose or know which type of oximeter your baby gets
- Above and below the range of 85%-95% each oximeter will always show the true oxygen saturation
- For babies who do not need extra oxygen, the study oximeter will often read up to 100%. That is quite normal
- All babies (whether in the study or not) will need occasional blood tests as part of routine care to check other things such as carbon dioxide

The pulse oximeter is a machine about the same size as a DVD player. It is kept on a shelf near the baby. This picture shows a display from a pulse oximeter. The baby's oxygen saturation reading is 91% and heart rate is 144

- Information will also be collected on your baby's antenatal and neonatal course and kept in a confidential way using code numbers. No reports from the study will identify you or your baby in any way.
- It's very important that we find out how your baby is doing at 2 years of age. When you go home, we'd like to keep in touch, so we will record your contact details. It's important to tell us if they change.
- When your baby is 2 years old (corrected for prematurity) he/she will be invited to be assessed by a paediatrician and have a formal test of development (the Bayley Test) and of vision.
- Most children will still be in routine paediatric follow-up at this time so the paediatric assessment will be at the time of a normal out-patient visit. The Bayley Test and vision assessment may require one or two extra visits and take 45 minutes and 30 minutes each.

DESCRIPTION OF INCONVENIENCES OR HAZARDS WHICH MIGHT BE EXPECTED:
We do not expect any difficulties at all with this study for your baby.

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- As noted the Bayley Test and vision assessment might require two extra visits. We can help with the expense of this, for example by providing a petrol voucher, if necessary

Participation:
Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part your baby will receive the usual care. If you do agree to take part you are free to withdraw your baby from this study at any time, without having to give a reason, and this will in no way affect your baby's care.

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If you have any questions about ACC, contact your nearest ACC office or the investigator.

Ethical approval:
This study has been approved by the Multi-Region Ethics Committee, which reviews national and multiregional studies.

IF YOU WANT TO KNOW MORE:
If you want to know anything further about this study (either now or at any later date) please feel free to ask.

Prof Brian Darlow	Principal investigator BOOST-NZ Paediatrician, Christchurch Women's Neonatal Unit Phone: 3644-699 : carries pager
Dr Glynn Russell	Paediatrician, Christchurch Women's Neonatal Unit Phone: 3644-699 : carries pager
Nicki McNeill/Trish Graham	Research Nurses BOOST-NZ Christchurch Women's Neonatal Unit Phone: 3644-742: has answerphone

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact a Health and Disability Services Consumer Advocate: phone 3777 501
Or free phone if residing out of town: 0800 377 766

CONSENT FORM

PROJECT TITLE: What oxygen saturation level should we target in very preterm infants? – a randomised controlled trial (RCT). The BOOST-NZ study

INVESTIGATORS: Professor Brian Darlow, Department of Paediatrics,
Christchurch School of Medicine and Health Sciences.
Dr Carl Kuschel, National Women's Health, Auckland City Hospital
Dr Michael Meyer, Middlemore Hospital
Dr Michael Hewson, Wellington Hospital
Dr Roland Broadbent, Dunedin Hospital
Dr Cynthia Cole, Harvard University, Boston

VENUE: Christchurch Women's Hospital, Christchurch; National Women's Health, Auckland; Middlemore Hospital; Wellington Women's Hospital; Dunedin Hospital

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STATEMENT BY PARENT:

I/we have read and understood the attached information sheets and have had the opportunity for discussion with a doctor. I/we am/are satisfied with answers I/we have been given. I/we understand that taking part in this study is voluntary (my/our choice) and that I/we may withdraw my baby from this study at any time, and this will in no way affect my baby's or my family's continuing or future health care in any way.

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I/we understand the compensation provisions for this study.
I/we have had time to consider whether to take part.
I/we know whom to contact if I have any questions about the study.
I/we wish to receive a summary of the results of the research. **Yes / No**

I/we give consent for my midwife / GP to be notified of my baby's participation in this research. **Yes / No**

I consent to my baby _____(baby's name) taking part in this study.

Signed:----------Print---------- Date: / /

----------Print---------- Date: / /

Doctor:----------Print---------- Date: / /

Request for Interpreter

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
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	Other languages to be added following consultation with relevant communities.		

2001 Census question about ethnicity:

Which ethnic group do you belong to?
Mark the space or spaces which apply to you.

- NZ European
- Māori
- Samoan
- Cook Island Maori
- Tongan
- Niuean
- Chinese
- Indian
- other (such as *DUTCH, JAPANESE, TOKELAUAN). Please state:*

Ko tēhea momo tāngata e whai pānga atu ana koe?
Tohua te katoa o raro nei e hāngai ana ki a koe.

- Pākehā
- Māori
- Hāmoa
- Māori Kuki Airani
- Tonga
- Niue
- Hainamana
- Īnia
- tētahi atu (pērā i *TATIMANA, HAPANĪHI, TOKELAU). Tuhia mai:*

Blansfield, Earl (NIH/NICHD) [E]

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Monday, May 13, 2013 7:55 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]
Subject: FW: FOIA Request - Case 41312
Attachments: FOIA Request.pdf

FYI

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Blansfield, Earl (NIH/NICHD) [E]
Sent: Monday, May 13, 2013 7:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Cornell, Susan (NIH/OD) [E]
Subject: FOIA Request - Case 41312

Good Morning Rose,

We received another FOIA request from Dr. Carome.

Please see the attached.

Thanks

Earl

Earl H. Blansfield
FOIA Coordinator
Eunice Kennedy Shriver National Institute of Child Health and Human Development/NIH
31 Center Drive, Rm. 2A32
Bethesda, MD. 20892
Phone - (301) 435-3457
Fax - (301)-496-7101

PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

May 10, 2013

Earl Blansfield
National Institute of Child Health and Human Development
Building 31, Room 2A32
9000 Rockville Pike
Bethesda, MD 20892

SENT BY EMAIL TO: earl.blansfield@nih.hhs.gov

Dear Mr. Blansfield:

On behalf of Public Citizen's Health Research Group (HRG), and pursuant to the Freedom of Information Act (FOIA), 5 U.S.C. 552 as amended, I hereby request the following documents:

All institutional review board-approved versions of the consent forms for each research institution involved in the conduct of the following studies being conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Neonatal Research Network.

(1) Evaluation of Systemic Hypothermia Initiated After 6 Hours of Age in Infants ≥ 36 Weeks Gestation With Hypoxic-Ischemic Encephalopathy: A Bayesian Evaluation (primary endpoints: death or moderate or severe disability);[1]

(2) A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for Extremely Low Birth Weight Infants With Necrotizing Enterocolitis or Isolated Intestinal Perforation (primary endpoints: death or neurodevelopmental impairment);[2]

(3) Optimizing Cooling Strategies at < 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy (primary endpoints: death or moderate to severe disability);[3]

(4) A Randomized Controlled Trial of the Effect of Hydrocortisone on Survival Without Bronchopulmonary Dysplasia and on Neurodevelopmental Outcomes at 22-26 Months of Age in Intubated Infants < 30 Weeks Gestation Age (primary endpoints: improvement in survival without physiologically defined moderate to severe bronchopulmonary dysplasia, and survival without moderate or severe neurodevelopmental impairment);[4]

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[1] http://clinicaltrials.gov/ct2/show/NCT00614744. Accessed April 12, 2013.
[2] http://clinicaltrials.gov/ct2/show/NCT01029353. Accessed April 12, 2013.
[3] http://clinicaltrials.gov/ct2/show/NCT01192776. Accessed April 12, 2013.
[4] http://clinicaltrials.gov/ct2/show/NCT01353313. Accessed April 12, 2013.

(5) Neurodevelopmental Effects of Donor Human Milk vs. Preterm Formula in Extremely Low Birth Weight Infants (primary endpoint: neurodevelopmental outcome; death is one of the secondary endpoints);[5]

(6) Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy? (primary endpoints: death or significant neurodevelopmental impairment);[6] and

(7) A Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Hypoxic-Ischemic Encephalopathy in Premature Infants 33-35 Weeks Gestational Age (primary endpoints: death or moderate or severe disability).[7]

If possible, please send me digital copies of these documents by email to mcarome@citizen.org.

Please send me documents as they become available rather than waiting to assemble all of the requested documents.

Public Citizen requests that all fees in connection with this FOIA request be waived in accordance with 5 U.S.C. § 552(a)(4)(A)(iii) because Public Citizen does not seek the records for a commercial purpose and disclosure "is in the public interest because it is likely to contribute significantly to public understanding of the operations or activities of the government." The requested records are not currently available to the public. We expect that the responsive records will reveal the NIH oversight process for clinical trials.

Public Citizen, which has 300,000 members and supporters, is a nonprofit research, litigation, and advocacy organization that represents the public interest before Congress, the executive branch, and the courts. It fights for openness and democratic accountability in government; for social and economic justice in globalization and trade policies; for strong health, safety, human subjects and environmental protections; and for safe, effective and affordable medicines and health care. It is composed, in part, by its Health Research Group. Public Citizen intends to share information received from this request with the public. It regularly publishes reports based upon information acquired through FOIA. Public Citizen disseminates its reports via publication, through its website, and through various newsletters that are distributed to consumers, lawyers, academics, and other interested parties free of charge. Public Citizen staff members also serve as a resource for the media and testify before Congress. Public Citizen, therefore, qualifies for a public interest fee waiver.

In addition, Public Citizen is entitled to a waiver of all search and review fees because it is a "representative of the news media" and, as a nonprofit organization, does not seek the requested records for a commercial purpose. As noted above, it regularly publishes reports and other products, which it disseminates via publications, its website, and various newsletters. It also

[5] http://clinicaltrials.gov/ct2/show/NCT01534481. Accessed April 12, 2013.
[6] http://clinicaltrials.gov/ct2/show/NCT01702805. Accessed April 12, 2013.
[7] http://clinicaltrials.gov/ct2/show/NCT01793129. Accessed April 12, 2013.

contributes to and maintains five active blogs, including Citizen Vox Blog, available at http://www.citizenvox.org/. As these facts demonstrate, Public Citizen qualifies as a representative of the news media because it "gathers information of potential interest to a segment of the public, uses its editorial skills to turn the raw materials into a distinct work, and distributes that work to an audience." 5 U.S.C. § 552(a)(4)(A)(ii).

If, however, a fee waiver is not granted, please advise me of the estimated cost of fulfilling the request before conducting any work that would result in an assessment of any fees to Public Citizen.

Thank you for your prompt attention to this request.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

mcarome@citizen.org
(202) 588-7781

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 12, 2013 2:02 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: FW: BOOST II NZ

Very sweet note from the pi.

-----Original Message-----
From: Brian Darlow [mailto:brian.darlow@otago.ac.nz]
Sent: Saturday, May 11, 2013 8:30 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: BOOST II NZ

Dear Kathy, Many thanks.
Yes, that is correct. Our hypothesis was that the lower target would be associated with decreased mortality or neurodevelopmental impairment at 24 months corrected age. In other words we hypothesised this saturation target might be safest overall. But we did not know precisely how the different components of the composite outcome would contribute.

Some might say, OK, so that means you thought the high saturation might have the worst outcome even including increased mortality. I think the answer is that we thought the range 85%-95% safest overall but within that range the lower end might give better outcomes than the higher end, but that we were in genuine equipoise about that. One of the 6 regional NICUs in New Zealand were convinced the lower target was better, were not in equipoise and did not join the trial.

Would babies in the trial have inceased risks over "Standard Care"? Clearly we believed not or we would not have started the trial. In fact our experience has been, in common with some published data, that babies in these sorts of trials are if anything likely to do better than similar baies outside the trial. My personal belief was (and probably still is) that careful monitoring to minimise wide fluctuations in saturation (and things such as blood pressure) may be more important than the precise target which is adopted. A clear protocol about tight control of saturation was a key part of the trial.

What is also missed in this debate is that talking with parents about the trial only ever occurred after talking with them about birth at 3 months premature and the fact that not all such babies will survive and some that do survive will have morbidities (problems) of various sorts. In New Zealand we have good population based information on the outcome and can give parents figures on the risks. But these figures are statistics and each baby is an individual who may have factors that will increase or decrease their chances of a certain outcome.
It is in this context that the Parent Information sheet, for this and other studies, needs to be viewed.

Kindest regards, Brian Darlow

From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
Sent: Sunday, 12 May 2013 9:29 a.m.
To: Brian Darlow
Cc: Higgins, Rosemary (NIH/NICHD) [E]

Subject: Re: BOOST II NZ

Dr Darlow
Thank you so much for sharing this document. In the background section there is mention of how low or high oxygen levels for extended periods of time may have consequences for the baby. These include mention of decreased survival.

In the description of the study it says that babies will be at no increased risk over normal treatment.

I have understood those background statements about survival to refer to historical studies below and above the range in boost and its sister studies. Is that a correct reading?

Our assumption is that there was no expectation of higher mortality in the study than in standard of care. Is that correct?

I really appreciate your input and also the work that you do to improve the care of these teeny babies

Thanks
Kathy Hudson
Deputy Director
NIH

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

On May 11, 2013, at 4:45 PM, "Brian Darlow" <brian.darlow@otago.ac.nz> wrote:

> Dear Rose, Thanks. Yes, good to see you at PAS. An interesting meeting!.
> My apologies, I thought our PIS and consent form had gone to all NeOPRoM members. It as attached - each site had their own institutional heading.
>
> Thanks for sending the updated AAP recommemdations - the section on Sat targets is very sensible and clearly written. Very helpful.
>
> Kindest regards
>
> _____
> From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
> Sent: Sunday, 12 May 2013 2:57 a.m.
> To: Brian Darlow
> Cc: Hudson, Kathy (NIH/OD) [E]
> Subject: BOOST II NZ
>
> Hi Brian -
> Nice to see you at PAS.
> Would you mind sharing the BOOST II NZ sample consent with us at NIH?
> Thanks in advance for your help.
> With best regards,

> Rose
> Rosemary D. Higgins
> Program Scientist for the NICHD Neonatal Research Network <BOOST NZ PI
> Form-Final-Chch.doc>

From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: mettanalysis
Date: Sunday, May 12, 2013 8:48:01 PM

Hi rose
Enjoy your days off
I will be at the american thoracic society meeting in philly until may 22 so will try to reach you after that
Carol

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 10, 2013 04:41 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Re: mettanalysis

I am on (b)(6)
Perhaps later next week?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Friday, May 10, 2013 04:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: mettanalysis

Thanks Rose.
Would love to talk with you on Monday, if you have time between 8-3?

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 10, 2013 9:10 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: mettanalysis

Here is the paper – happy to discuss

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Friday, May 10, 2013 9:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: mettanalysis

Dear Rose,
Hope you enjoyed PAS, lots of good science this year.
I heard B. Schmidt's presentation of COT and Ben Stenson's on the metaanalysis of oxygen sat targets.
Have been able to find Barbara's JAMA paper, but not the Stenson 2013 paper---do you have a link to it?

Seemed that Barbara was making a point about (b)(5)
(b)(5) What is your interpretation of her results and the meta-analysis?

Hope the hype has settled down finally,
Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: Re: note to ohrp
Date: Sunday, May 12, 2013 12:54:13 PM

Not sure- but they really are r(b)(5)

(b)(5)

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 12, 2013 12:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: Re: note to ohrp

Do u think (b)(5) I don't think we have (b)(5)
(b)(5)..

Maybe I am too grumpy.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 12, 2013, at 12:16 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> This looks good-are your going to send along the actual consent form that Brian Darlow shared?
>
> Thanks for all your help with this.
> Rose
> Rosemary D. Higgins
> Program Scientist for the NICHD Neonatal Research Network
>
> **From:** Hudson, Kathy (NIH/OD) [E]
> **Sent:** Sunday, May 12, 2013 11:57 AM
> **To:** Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
> **Subject:** note to ohrp
>
> Comments welcome....

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 12, 2013 11:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: note to ohrp
Attachments: note to ohrp.docx

Comments welcome....

Page 1511 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1512 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: Re: bizarre language
Date: Saturday, May 11, 2013 1:57:22 PM

I have requested the BOOST NZ consent (a few hours ago). Given the time difference (11-13 hours), it may take a little while. We have the COT trial, BOOST II UK and Australia consents (none have mortality in the risk section).
Will keep folks posted!
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Saturday, May 11, 2013 01:49 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: bizarre language

We have requested the nz consent and I want to wait for that.

I would keep your chat with Howard pristine.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 11, 2013, at 1:45 PM, "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov> wrote:

> Very interesting indeed. I think this should be brought to the attention of Jerry, Howard, and Andrea.
>
> I was planning to reach out to Howard this weekend - (b)(5)
> (b)(5)
>
> FC

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 11:37 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: bizarre language

I clearly need a (b)(6)

(b)(6)

Here is my current obsession.

1. In the latest version of the ohrp letter to uab, (b)(5)

(b)(5)

(b)(5) Do you agree?

4. Thus, I think (b)(5)

(b)(5)

I think this makes (b)(5)

(b)(5)

Thoughts?

<< File: BOOST-NZ information_consent[1].pdf >>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: bizarre language
Date: Saturday, May 11, 2013 6:15:45 AM

I agree- for (b)(5) (in my view) (b)(5)

(b)(5)

As far as the parent brochures are concerned, many of the neonatal network sites have these for clinical care. These are generally not quoted in peer review literature.

I still disagree with (b)(5)

(b)(5)

I respectfully disagree with the (b)(5)

(b)(5)

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 11:37 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: bizarre language

I clearly need a (b)(6)

Here is my current obsession.

1. In the latest version of the ohrp letter to uab, (b)(5)

(b)(5)

(b)(5)

4. Thus, I think (b)(5)

(b)(5)

Thoughts?

<<BOOST-NZ information_consent[1].pdf>>

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 10, 2013 8:33 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: letter to OHRP

I can continue to try to provide facts.

Our PI at Brown, Dr. Abbot Laptook was interviewed by NPR Rhode Island earlier today. The article can be found at: http://www.ripr.org/post/women-infants-researcher-counters-critics-premature-baby-study

He called me and and told me the reporter wanted to know his thoughts on Public Citizen's viewpoint - Abbot was gracious (as always). and didn't provide comment

I also heard that Journal of Pediatrics has an editorial in progress.

thanks for sharing

Rose
Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20592
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 8:11 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: letter to OHRP

Interesting hhs never shared this letter with us.... Should we (b)(5)
(b)(5)
Thoughts?

-----Original Message-----
From: Lantos, John [mailto:jlantos@cmh.edu]
Sent: Friday, May 10, 2013 5:43 PM
To: Hudson, Kathy (NIH/OD) [E]

Subject: letter to OHRP

Kathy,

And here is a letter I sent to OHRP, with a copy to Secretary Sibelius. I haven't heard back.

J
John D. Lantos M.D.
816-701-5284

Are you interested in an on-line certificate program in Pediatric Bioethics?
Visit the the CMH Bioethics Center web page: http://www.childrensmercy.org/cmbc.
We have a few spots left for 2013-14.

From: Lantos, John
Sent: Friday, April 19, 2013 13:13
To: 'jerry.menikoff@hhs.gov'; 'lisa.buchanan@hhs.gov'
Cc: 'Kathleen.Sebelius@hhs.gov'
Subject: Please apologize and correct your misrepresentations

April 19, 2013,

Dear Drs. Menikoff and Buchanan,

I think that you have an obligation to the parents of babies who were in the SUPPORT study, and to the parents of babies who might be enrolled in future studies, to clarify to the public, in a press release, that there was no harm done to babies who were in the SUPPORT study. I think that you should also publically repudiate Public Citizen for the use that they have made of your letter to UAB and the implication that not only the SUPPORT study but all studies of the NICHD neonatal network should be halted. Letting your letter to UAB stand as written in the public record has the potential to harm many babies by leading their parents to the misleading judgment that research is riskier than it is.

In particular, you write:

"It would have been appropriate for the consent form to explain (i) that the study involves substantial risks, and that there is significant evidence from past research indicating that the level of oxygen provided to an infant can have an important effect on many outcomes, including whether the infant becomes blind, develops serious brain injury, and even possibly whether the infant dies; (ii) that by participating in this study, the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received, though it is not possible to predict what that change will be; (iii) that some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind; and (iv) that the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death."

Number (ii) is true. Numbers (i), (iii) and (iv) are not. The study did not involve substantial risks compared to the alternative – that is, oxygen levels determined based on clinical judgment. The investigators didn't believe this to be true when the study was designed. And they were right. The results from the study showed that it wasn't true. You should acknowledge that. The infants in the higher oxygen group did not have a greater risk of going blind, compared to either conventional therapy or, as it turned out, compared to the lower oxygen group. (They had higher rates of retinopathy, but rates of blindness were not different.) You should acknowledge that. The level of oxygen was not thought to increase the risk of brain injury or death compared to conventional therapy or in a comparison of the two arms of the trial. And it didn't.

The Editors of the New England Journal of Medicine (http://www.nejm.org/doi/full/10.1056/NEJMe1304996?query=featured_home) and the investigators (http://www.nejm.org/doi/full/10.1056/NEJMc1304827?query=featured_home) vigorously dispute your interpretations of the study and the results. http://www.nejm.org/doi/full/10.1056/NEJMe1304996?query=featured_home

Allowing your misleading statements to stand, in the public record, will mislead parents, lead them to decide not to participate in NICHD trials, which might be worse for the babies and worse for future babies. You owe it to the doctors, and to America's children to apologize for and correct these statements. Please do the right thing.

John Lantos M.D.

John Lantos M.D.

Director, Children's Mercy Bioethics Center

Children's Mercy Hospital

2401 Gilham Rd.

Kansas City, MO 64108

816-701-5283 (phone)

816-701-5286 (fax)

jlantos@cmh.edu<mailto:jlantos@cmh.edu>

Assistant: Mary Ellen Hudson, 816-701-5284

Visit the Children's Mercy Bioethics Center web page<http://www.cmh.edu/cmbc> (http://www.childrensmercy.org/cmbc) for general information and a link to the application for the 2013-2014 CMBC Certificate Program in Pediatric Bioethics. The deadline for applications is Friday, March 1st! We will consider applications as they are received.

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 10, 2013 12:58 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]
Subject: COT Trial consent
Attachments: COTHUPIRB.pdf

Hi
I have received the COT (Canadian Oxygen Trial) consent form from Dr. Barbara Schmidt. Under the risks, mortality does not appear.

Rose

University of Pennsylvania
Office of Regulatory Affairs
Yvonne Higgins, Director Human Research Protections
Emma Meagher, MD, IRB Executive Chair
3624 Market St., Suite 301 S
Philadelphia, PA 19104-6006
Ph: 215-573-2540/ Fax: 215-573-9438
INSTITUTIONAL REVIEW BOARD
(Federalwide Assurance # 00004028)

15-Feb-2008

BARBARA K SCHMIDT
NEONATOLOGY
RAVDIN 8
HUP 4283
Pdf sent by email to Barbara.schmidt@uphs.upenn.edu and aasma.chaudhary@uphs.upenn.edu

PRINCIPAL INVESTIGATOR	: BARBARA K SCHMIDT
TITLE	: Canadian Oxygen Trial
SPONSORING AGENCY	: CANADIAN INSTITUTE OF HEALTH RESEARCH
PROTOCOL #	: 807454
REVIEW BOARD	: IRB #2

Dear Dr. Schmidt:

IRB approval has been given to the above referenced protocol as of **15-Feb-2008**. This study will be due for **continuing review on or before 14-Feb-2009.**

This study has been determined to be minimia risk and future reviews will take place under the expedited mechanism.

Approval by the IRB does not necessarily constitute authorization to initiate the conduct of a human subject research study.

Principal investigators are responsible for assuring final approval from other applicable school, department, center or institute review committee(s) or boards has been obtained. This includes, but is not limited to, the University of Pennsylvania Cancer Center Clinical Trials Scientific Review and Monitoring Committee (CTSRMC), Clinical and Translational Research Center (CTRC) review committee, CAMRIS committee, Institutional Bio-safety Committee (IBC), Environmental Health and Radiation Safety Committee (EHRS), and Standing Conflict of Interest (COI) Committee. Principal investigators are also responsible for assuring final approval has been obtained from the FDA as applicable, and a valid contract has been signed between the sponsor and the Trustees of the University of Pennsylvania. If any of these committees require changes to the IRB-approved protocol and informed consent/assent document(s), the changes must be submitted to and approved by the IRB prior to beginning the research study.

If this protocol involves cancer research with human subjects, biospecimens, or data, you may not begin the research until you have obtained approval or proof of exemption from the Cancer Center's Clinical Trials Review and Monitoring Committee.

The revisions, in response to a full board review, were reviewed and approved by Dr. Emma Meagher, Executive Chair of the IRB (or her authorized designee), using the expedited procedure set forth in 45 CFR 46.110(b).

The following documents were included in this review:
- correspondence dated 2/13/2008
- informed consent
- protocol summary v. 2/13/2008

When enrolling subjects at a site covered by the University of Pennsylvania's IRB, a copy of the IRB approved informed consent form with the IRB approved from/to stamp must be used unless a waiver of written documentation of consent has been granted.

The IRB has received a HIPAA Authorization Form which will be used for all study subjects, which is presumed to be accurate. Disclosure of any protected health information outside the constraints of the authorization is prohibited. It is mandatory that you obtain a new authorization or submit a waiver request to change the current terms of the disclosure authorization in any way.

If you have any questions about the information in this letter, please contact the Regulatory Affairs administrative staff. Contact information is available at our website: http://www.upenn.edu/regulatoryaffairs/Contact.html.

Thank you for your cooperation.

Sincerely,

IRB Administrator

UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

Department of Pediatrics

Neonatology and Newborn Services
Hospital of the University of Pennsylvania

PARENTAL INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Participant's Name: _____

Title: Efficacy and Safety of Targeting Lower Arterial Oxygen Saturations to Reduce Oxygen Toxicity and Oxidative Stress in Very Preterm Infants

Short Title: **Canadian Oxygen Trial (COT)**

Investigator: Barbara Schmidt, MD, MSc
Address: Division of Neonatology and Newborn Services
Hospital of the University of Pennsylvania
Ravdin 8, 3400 Spruce Street
Philadelphia, PA 19104
Office # : 215-662-3228
24 Hr # : 215-662-3884
IRB #:
Sponsor: McMaster University and the Canadian Institutes of Health Research

IRB APPROVAL DATE: 02-15-2008
EXPIRATION DATE: 02-14-2009

Thank you for taking time to read this when so much is happening to your baby. We know it is a difficult time for you.

Why am I being asked to have my baby participate in the study?

You and your baby are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want your baby to participate. If you choose not to have your baby participate, there will be no loss of benefits to which your baby is otherwise entitled. Before you can make your decision, you will need to know what the study is about and the possible risks and benefits of being in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team about this form. If you decide to have your baby participate, you will be asked to sign this form.

What is the purpose of the study?

The purpose of this study is to understand which blood oxygen level (oxygen saturation) is better for very premature babies. A premature baby's eyes, lungs or brain can be harmed by too much or too little oxygen in the blood for long periods. At present, doctors and nurses in different hospitals around the world usually aim to keep a very premature baby's blood oxygen saturation somewhere between 85% and 95%. We want to find out if the lower or upper part of this range is better.

This study has been very carefully designed to ensure that each baby receives the best possible care while we understand which oxygen saturation level is better. It is approved and funded by the Canadian Institutes of Health Research and is led by doctors who are experts in the care of very premature babies.

How long will my baby be in the study? How many other babies will be in the study?

Your baby will remain in the study for the duration of his/her hospital admission in the Intensive Care Nursery (ICN) at the Hospital of the University of Pennsylvania (HUP) and until the date of the follow up appointment at the end of the second year of life. This follow-up appointment will be conducted at the Special Babies Clinic affiliated with HUP. The study will enrol 1200 very premature babies from major hospitals in Canada, the United States, Europe, Israel and Argentina. This study is part of a worldwide study of over 6000 babies.

What does the study involve?

We continuously monitor the oxygen level in the blood of a baby with an oximeter (oxygen saturation monitor) on a hand or foot. Oximeters are used every day, and all day, in the care of each and every very premature baby. Our study is using the current standard of care for premature babies. The research component of the study involves the use of study oximeters instead of the oximeters normally used in the Intensive Care Nursery. These study oximeters will monitor the oxygen saturation in premature babies enrolled in the study.

The oximeter is connected to a small sensor placed on the baby's hand or foot. The sensor shines a red light into the tissues and measures the oxygen saturation and heart rate every few seconds. Blood oxygen saturation changes every few seconds. It cannot be controlled exactly. Babies who join the study will be allocated a study oximeter at random (like tossing a coin). The oximeters are all the same type but have been slightly altered to two different ranges.

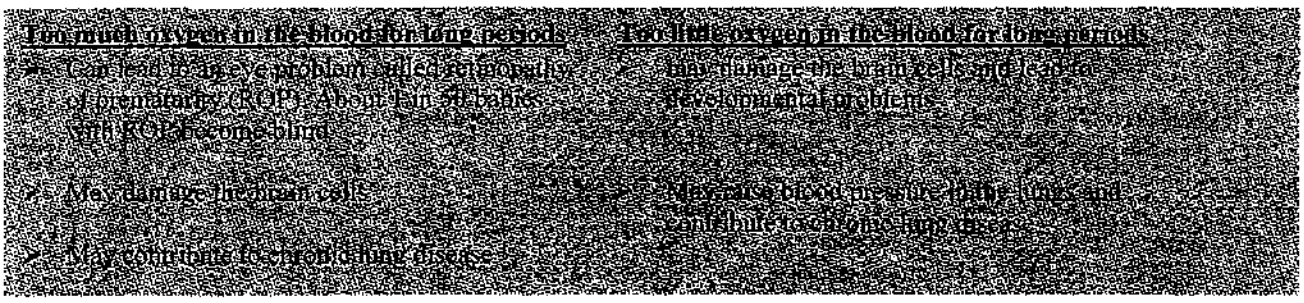
Your baby will have an actual oxygen saturation target range of either 85% – 89% or 91% –95%. Both levels are commonly used in premature babies. Neither you nor the doctors or nurses can choose or know which type of oximeter your baby gets. This type of masked randomised trial is the best way to find out which oxygen saturation is better for very premature babies in the future.

Above or below the range of 85% - 95% each oximeter will always show the true oxygen saturation. For babies who do not need extra oxygen, the study oximeter will often read up to 100%. That's quite normal. If your baby is transferred to CHOP for a clinically indicated procedure, your baby will be able to continue their participation in this study while there.

When your baby is nearly 2 years old we will arrange for you and your child to be seen in the Special Babies Clinic. This clinic is affiliated with the Hospital of the University of Pennsylvania (HUP). Its medical Director is Dr. Hallam Hurt. All extremely preterm babies are routinely followed in this clinic to check how well they develop and grow. At this visit we will perform a physical exam and administer a special test (Bayley Scales of Infant Development version 3). This will tell us how your child has learnt to walk, talk and play.

What are the possible risks of taking part in the research?

Too much or too little blood oxygen might affect long-term health and development. These risks exist whether or not your baby is in the study. This study is not altering the standard of care for your baby. The risks associated with this study are similar to the risks that exist in current medical practise.



If your doctor was sure that one of the oxygen targets was better than the other (for whatever reason) your baby would not be asked to join this study.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you and your baby. This includes information that, once learned, might cause you to change your mind about your baby's participation in the study. We will notify you as soon as possible if such information becomes available. An independent group of experts will review the progress of the study and if a result comes out that one oxygen saturation range is clearly better than the other the study will be stopped.

What are the possible benefits of the study?

This study will increase medical knowledge and may improve the outcome for premature babies in the future. This may not directly benefit your baby. Babies may benefit from the extra checks during the study.

Compensation and Costs

You will not be charged for any tests or procedures involved in this study. In addition, we will provide a small amount of money during the follow up visit to cover your costs of travel and parking.

Injury/ Compensation

Your baby's participation in this study is limited to the monitoring of the oxygen saturation by the study oximeters and the completion of the follow up appointment. The monitoring of your baby's oxygen saturation will only take place during the baby's hospital admission in the Intensive Care Nursery. In the event that you believe your baby has suffered any physical injury as a result of participation in this research program, please contact the Principal Investigator listed on page one of this form. You may also contact the Director of Regulatory Affairs of the University of Pennsylvania Health System at 215-898-2614, where the matter may be reviewed with you, resources may be identified that are available to you and your baby, and further information may be provided as to how to proceed.

If your child is injured because of this study, Hospital of the University of Pennsylvania can provide medical care but you or your insurance company will have to pay for that care. If your baby is injured or harmed due to his or her participation in this study, treatment for your baby will be made available. No other medical treatment or financial compensation, including but not limited to, money for lost wages or earnings or for pain and suffering, will be provided to you, your baby, or anyone else.

When is the Study over?

This overall study is expected to end after all the participants (all the babies in the study) have completed all visits, and all information has been collected. In regards to your baby's participation in the study, the study will end after your baby's follow-up appointment is completed at the Special Babies Clinic.

Can I remove my baby from the study before it ends?

If you decide to permit your child to participate, you are free to withdraw your consent and to discontinue your child's participation at any time, by contacting Dr. Barbara Schmidt, whose contact details are listed on the first page of this form. If you do not want your child to take part, or if you decide to withdraw your baby during the study, this will not affect your baby's medical treatment or your relationship with the medical staff at the Hospital. However, if you do withdraw your baby from the use of the study oximeter, we will ask your permission to collect data regarding your baby's stay in the intensive care unit and to follow your baby's progress during the first 2 years.

Confidentiality

Every effort will be made to keep your baby's medical records confidential (secret). Only people involved in the study and other authorised persons will have access to the data and the baby's medical records. The Principal Investigator is not required to release research information to you that is not part of your medical record.

Any study information that can identify you or your child will be kept confidential. It would only be disclosed with your permission or if required by law. Study data will be stored at the Hospital of the University of Pennsylvania and at the Coordinating and Methods Centre in Hamilton, Ontario, Canada. Participants will not be identified in any publication.

Who can I call with questions and complaints?

If you have any complaints about the study or have questions about your baby's rights as a research subject, you should speak with the Principal Investigator (Dr. Barbara Schmidt). If a member of the research team cannot be reached or you may want to speak with someone other than those working on the study, you may contact the Office of Regulatory Affairs with any questions, concerns or complaints at the University of Pennsylvania Health System at 215-898-2614, where the matter may be reviewed with you and further information may be provided as to how to proceed. You can contact Dr. Barbara Schmidt if you have any questions or concerns arising from taking part in this research by phoning at 215-662-3228 during working hours or 215-662-3884 after normal working hours, email is Barbara.Schmidt@uphs.upenn.edu.

Subject/Patients Rights

You have the right to ask any questions concerning the potential and/or known hazards of this study at any time. You also understand that you will be informed of any significant new information pertaining to safety that might affect your willingness for your baby to continue participation in this study.

HIPAA AUTHORIZATION SECTION

This authorization section gives more detailed information about how your baby's personal health information may be used and disclosed by the University of Pennsylvania Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What personal health information is collected and used in this study and might also be disclosed?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, date of birth, parental email addresses (if available)
- Personal and family medical history
- Current and past medications or therapies
- Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- Results of tests and procedures you will undergo during this research study as described in the informed consent form.

Why is your personal contact and health information being used?

Your personal contact information is important for the research team to contact you during the study. Your baby's personal health information and results of tests and procedures are being collected as part of this research study. In some situations, your baby's personal health information might be used to help guide your medical treatment.

Which of our personnel may use or disclose your baby's personal health information?

The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- A member of the IRB or ethic committee that has approved the study for your baby
- The Children's Hospital of Philadelphia
- Coordinating and Methods Centre in Hamilton, Ontario, Canada.
- The Special Babies Clinic affiliated with the Hospital of the University of Pennsylvania

Who, outside of UPHS and the School of Medicine, might receive your baby's personal health information?

As part of the study, the Principal Investigator, the study team and others listed above, may disclose your baby's personal health information, including the results of the research study tests and procedures in addition to your personal contact information. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- Dr. Barbara Schmidt and members of her research team at McMaster University in Canada
- Canadian Institute of Health Research
- Others: Children's Hospital of Philadelphia; your baby's personal health information from this clinical trial may be disclosed to your referring institution in order to better manage your baby's care; Special Babies Clinic affiliated with UPHS; and your baby's primary care physician

Regulatory and safety oversight organizations

- The Office of Human Research Protections
- The Study Data and Safety Monitoring Board

Once your baby's personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your baby's active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose your baby's personal health information?

Your authorization for use of your baby's personal health information for this specific study does not expire. Your baby's information may be held in a research repository (database) for 25 years after the completion of the study. However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Will you be able to access your baby's records?

During your baby's participation in this study, you might not be able to access some or all of your baby's medical records. For example, access to portions of your baby's medical records may be denied in studies where your knowledge of study results included in such records could affect the reliability of the study. You will have access

to your baby's medical record information when the study is over or earlier, if possible. The Principal Investigator is not required to release research information to you that is not part of your baby's medical record.

Can you change your mind?

Yes, at any time you may withdraw your approval to allow the use and disclosure of your baby's personal health information as described here. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your baby's personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your baby's personal health information, your baby will also be withdrawn from the research study.

You will be given a copy of this Parental Informed Consent and HIPAA Authorization form describing you and your baby's confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

By signing this document you are permitting the UPHS and the School of Medicine to use and disclose personal health information collected about your baby for research purposes as described above.

Parental Informed Consent and HIPAA Authorization Form

Efficacy and Safety of Targeting Lower Arterial Oxygen Saturations to Reduce Oxygen Toxicity and Oxidative Stress in Very Preterm Infants

I,_____
Name of Parent/Guardian (please print)

of_____
Address of Parent/Guardian (please print)

have read and understood the information for parents on the above named research study and have discussed it with _____ I am aware of the procedures involved in the study, including any inconvenience, risk, discomfort or side effect, and of their implications. I freely choose to take part in this study and understand that I can change my mind at any time without compromising the medical care and treatment that my child receives in the neonatal unit. I also understand that the research study is strictly confidential.

I hereby agree for my child _____ to take part in this research study.
Baby's Name (please print)

Signature of parent/guardian:_____ Date:___/___/____

Name of person obtaining consent:_____
(Please print)

Signature of person obtaining consent:_____Date:___/___/____

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Zaterka-Baxter, Kristin"
Subject: RE: REquested items
Date: Friday, May 10, 2013 9:15:00 AM

Yes
Thanks
Rose

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From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, May 10, 2013 9:15 AM
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Subject: RE: REquested items

Hi,

So this is the letter you were looking for in you VM, correct?

Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 10, 2013 8:30 AM
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Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Bock, Robert (NIH/NICHD) [E]
Subject: REquested items

Hi
Folks have asked for the Masimo letter which is attached. I have also attached the new (October 2012) oxygen management section from the AAP's Guidelines for Perinatal Care.

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nfiner@ucsd.edu"; "Yvonne Vaucher"; "richard.ehrenkranz@yale.edu"; "Roger Faix (Roger.Faix@hsc.utah.edu)"; "moshea@wfubmc.edu"; ""Duara, Shahnaz" (SDuara@med.miami.edu)"; "dale_phelps@urmc.rochester.edu"; "Frantz, Ivan"; " (EMcGowan@tufts-nemc.org)"; "srhintz@stanford.edu"; " (suhas.kallapur@cchmc.org)"; "Abbot Laptook (alaptook@wihri.org)"; "Abhik Das (adas@rti.org)"; "Ambal (ambal@uab.edu)"; "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)"; "barbara_stoll@oz.ped.emory.edu"; "bpoindex@iupui.edu"; "carl_dangio@urmc.rochester.edu"; "Carlton, David P"; "cotte010@mc.duke.edu"; "dstevenson@stanford.edu"; "dwallace@rti.org"; "Ed Bell (edward-bell@uiowa.edu)"; "epidb008@mc.duke.edu"; "Greg Sokol (gsokol@iupui.edu)"; "Haresh Kirpalani (KIRPALANIH@email.chop.edu)"; "John Barks"; "Jon.E.Tyson@uth.tmc.edu"; "Kennedy, Kathleen A"; "Krisa Van Meurs (vanmeurs@stanford.edu)"; "Kristi Watterberg (kwatterberg@salud.unm.edu)"; "Kurt Schibler [kurt.schibler@cchmc.org]"; "Luc Brion (luc.brion@utsouthwestern.edu)"; "Martin Keszler (mkeszler@wihri.org)"; "mcw3@po.cwru.edu"; "Meena Garg (mgarg@mednet.ucla.edu)"; "Nelin, Leif"; "Pablo.Sanchez@UTSouthwestern.edu"; "Polin, Richard"; "Robin Ohls (rohls@salud.unm.edu)"; "ronnie_guillet@urmc.rochester.edu"; "Satyan Lakshminrusimha"; "Schmidt, Barbara (Neonatology)"; "Seetha Shankaran "; "Sood, Beena [bsood@med.wayne.edu]"; "Truog, William (MD)"; "Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU)"; "Wally Carlo (wacarlo@uab.edu)"
Cc: Archer, Stephanie (NIH/NICHD) [E]; " (mcunningham@rti.org)"; " (kzaterka@rti.org)"; "Petrie, Carolyn"; Bock, Robert (NIH/NICHD) [E]
Subject: REquested items
Date: Friday, May 10, 2013 8:29:00 AM
Attachments: Safety Letter Masimo7_01.pdf
Guidelines for Perinatal Care 7-OXYGEN.docx

Hi

Folks have asked for the Masimo letter which is attached. I have also attached the new (October 2012) oxygen management section from the AAP's Guidelines for Perinatal Care.

Thanks

Rose

Rosemary D. Higgins, MD
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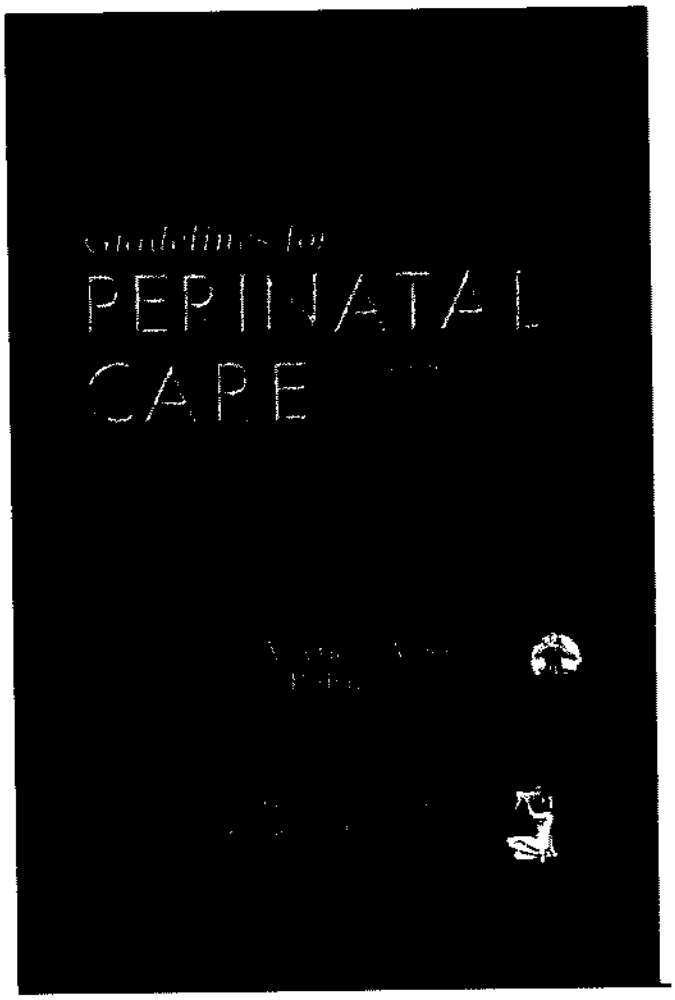

Guidelines for Perinatal Care was developed through the cooperative efforts of the American Academy of Pediatrics (AAP) Committee on Fetus and Newborn and the American College of Obstetricians and Gynecologists' (the College) Committee on Obstetric Practice. The guidelines should not be viewed as a body of rigid rules. They are general and intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

Library of Congress Cataloging-in-Publication Data

Guidelines for perinatal care / American Academy of Pediatrics [and] the American College of Obstetricians and Gynecologists.—7th ed.
p. ; cm.
Perinatal care
Includes bibliographical references and index.
ISBN 978-1-581B-734-0 (AAP) — ISBN 978-1-934984-17-8 (ACOG)
I. American Academy of Pediatrics. II. American College of Obstetricians and Gynecologists.
III. Title: Perinatal care.
[DNLM: 1. Perinatal Care—standards—United States—Practice Guideline. WQ 210]

618.3'206—dc23
2012009328

ISBN: 978-1-581B-734-0 AAP
ISBN: 978-1-934984-17-8 the College

Orders to purchase copies of *Guidelines for Perinatal Care* or inquiries regarding content can be directed to the respective organizations:

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Chapter 9

Neonatal Complications and Management of High-Risk Infants

This chapter highlights some of the common complications encountered in the care of high-risk infants and, whenever possible, provides an evidence-based approach to management.

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assessments using a standardized abstinence instrument.

Respiratory Complications

Oxygen Therapy

The hazards associated with administration of supplemental oxygen to preterm infants have been recognized for many years. Studies conducted in the 1950s indicated that prolonged unmonitored oxygen therapy was associated with increased rates of retinopathy of prematurity (ROP), formerly called retrolental fibroplasia. This discovery led to widespread restriction of oxygen therapy, which caused a marked decrease in ROP but an increase in cerebral palsy and mortality. Current practice recommends supplemental oxygen as needed, based on objective monitoring of oxygenation. Clinical assessment of physical signs to determine the amount of supplemental oxygen needed may be useful for short periods, emergencies, or abrupt clinical changes, but should not be the basis for ongoing supplemental oxygen therapy.

Supplemental oxygen can be delivered via endotracheal tube, mask, oxygen hood, nasal prongs, or cannula. Except in emergency situations, supplemental oxygen should be warmed and humidified, and the concentration or flow should be monitored and regulated. Orders for oxygen therapy should include desired ambient concentration, flow, or both. The concentration or flow rate of oxygen should be checked routinely. Orders should be written to adjust fraction of inspired oxygen (FIO_2) or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional guideline

for ordering, delivering, and documenting oxygen therapy and monitoring. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations.

An important development in the care of infants who require oxygen therapy is the ability to monitor oxygenation continuously with noninvasive techniques. The pulse oximeter measures the percentage of hemoglobin saturated with oxygen. Throughout most of the oxygen-hemoglobin dissociation curve, pulse oximetry will closely predict Pa_{O_2} when adjustments are made for the presence of fetal hemoglobin, and it is an excellent continuous monitor of oxygenation; however, at saturations greater than 96%, the Pa_{O_2} may be extremely high. The transcutaneous oxygen analyzer provides an indirect measurement of Pa_{O_2}. This device has the potential advantage of monitoring for high Pa_{O_2}; however, the heated membrane may cause burns, and the membrane may not read accurately because of poor perfusion or skin thickness, and it has been largely replaced by oximetry.

Continuous measurement of pulse oximetry combined with periodic measurement of Pa_{O_2} in samples from an umbilical or peripheral artery catheter is the most complete method of monitoring oxygen therapy. In infants whose condition is unstable, noninvasive measurements should be correlated with Pa_{O_2} as often as every 8–24 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and Pa_{CO_2}. In infants whose condition is stable, correlation with arterial blood gas samples may be performed when clinically indicated.

In the absence of an indwelling arterial catheter, arterialized capillary sampling provides reasonable estimates of arterial pH and Pa_{CO_2} if perfusion to the extremity is not compromised. Although Pa_{O_2} is not accurately estimated in arterialized capillary samples, the combined use of continuous oxygen saturation monitoring and intermittent capillary arterialized blood gases can guide oxygen therapy. In this circumstance, oxygen saturation should not be allowed to remain above 95%, as previously described, particularly in preterm infants at risk of ROP.

The use of either pulse oximetry or transcutaneous oxygen measurement may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are also useful in monitoring oxygen therapy in infants who are recovering from respiratory distress or who require long-term supplemental oxygen. Pulse oximetry is particularly advantageous for long-term monitoring of oxygen therapy

because transcutaneous oxygen measurements underestimate oxygenation in older infants with BPD and may cause burns.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should be used for specific indications, such as cyanosis, low Pa_{O_2}, or low oxygen saturation.
- For infants who require oxygen therapy for acute care, measurements of blood pH and Pa_{CO_2} should accompany measurements of Pa_{O_2}. In addition, a record of blood gas measurements, noninvasive measurements of oxygenation, details of the oxygen delivery system (eg, ventilator, continuous positive airway pressure, nasal cannula, hood, mask, settings), and ambient oxygen concentrations (Fi_{O_2}, liter of flow per minute, or both) should be maintained.
- The optimal range for oxygen saturation and Pa_{O_2} that balances tissue metabolism, growth and development, and toxicity has not been elucidated for preterm infants receiving supplemental oxygen. Data from cohort studies initially suggested that lower saturation ranges may decrease ROP. However, three RCT's demonstrated that although a target saturation range of 85–89% was associated with a decrease in severe ROP, it also was associated with an increase in mortality, compared with a target saturation range of 91–95%. These findings resulted in early study closure of two of these three studies, and a recommendation to target a saturation range higher than 85–89%. Of note, even with careful monitoring, oxygen saturation and Pa_{O_2} often fluctuate outside specified ranges, particularly in infants with cardiopulmonary disease.
- Regular and periodic (every 1–4 hours) measurement and recording of the concentration of oxygen delivered to the infant receiving supplemental oxygen is recommended.
- Except for an emergency situation, air–oxygen mixtures should be warmed and humidified before being administered to infants.

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is associated with surfactant deficiency and typically occurs in preterm infants, but may occasionally be seen in term infants, particularly in the setting of maternal diabetes. Multiple randomized controlled trials have demonstrated the benefits of surfactant replacement therapy, including reduction in the severity of RDS, decrease in pulmonary complications (eg, air leak), and improvement in survival. Surfactant therapy does not change

immunizations (see also "Immunization" in Chapter 6).

Retinopathy of Prematurity

A myriad of factors, including but not limited to hyperoxia, may contribute to the pathogenesis of ROP. Prematurity; low birth weight; multiple gestation; severity of illness; prolonged ventilatory support (especially when accompanied by episodes of hypoxia and hypercapnia); and clinical conditions, including acidosis, shock, sepsis, apnea, anemia, chronic lung disease, intraventricular hemorrhage, patent ductus arteriosus, and vitamin E deficiency also have been associated with retinopathy of prematurity.

To date, a safe level of PaO_2 in relation to retinopathy of prematurity has not been established, perhaps because multiple other factors, such as those listed previously play a part in its pathogenesis. Retinopathy of prematurity has occurred in preterm infants who have never received supplemental oxygen therapy and in infants with cyanotic congenital heart disease in whom PaO_2 levels never exceeded 50 mm Hg. Conversely, ROP has not developed in some preterm infants after prolonged periods of hyperoxemia. Data have demonstrated no additional progression of active prethreshold retinopathy of prematurity when supplemental oxygen was administered at pulse oximetry

saturations between 96% and 99%. Further, continuous, close monitoring of transcutaneous oxygen tension has not resulted in a decrease in the incidence of ROP when compared with intermittent transcutaneous monitoring. On the basis of published data, the following statements regarding ROP and oxygen use are warranted:

- Retinopathy of prematurity is not preventable in some infants, especially extremely premature infants.
- Many factors other than hyperoxia contribute to the pathogenesis of retinopathy of prematurity.
- Transient hyperoxemia alone cannot be considered sufficient to cause retinopathy of prematurity.
- Strict adherence to existing guidelines for supplemental oxygen therapy will not completely prevent complications or adverse effects.

Screening and Initial Examination

An ophthalmologist with sufficient knowledge and experience in retinopathy of prematurity and the use of binocular indirect ophthalmoscopy should examine the retinas of all preterm infants born at 30 weeks of gestation or less or weighing less than 1,500 g at birth, as well as selected infants weighing 1,500–2,000 g at birth with an unstable clinical course and who are thought to be at risk by their attending pediatrician or neonatologist. Sterile instruments should be used to examine each infant in order to avoid possible cross contamination of infectious agents. Pretreatment of the eyes with a topical anesthetic agent, such as proparacaine may minimize the discomfort and systemic effect of this examination. Consideration also may be given to the use of nonpharmacologic pain management interventions, such as pacifiers and oral sucrose.

Table 9-3 presents a suggested schedule for timing of initial eye examinations based on postmenstrual age and chronologic (postnatal) age. This schedule was designed to detect retinopathy of prematurity before it progresses to retinal detachment and to allow for earlier intervention, while minimizing the number of potentially traumatic examinations. The timing of follow-up examinations is best determined from the findings of the first examination, using the International Classification of Retinopathy of Prematurity (see also "Treatment and Follow-up Care" later in this section). One examination is sufficient only if it unequivocally shows the retina to be fully vascularized in each eye.

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MASIMO®
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Tel: 949-297-7000
Fax: 949-297-7001

June 30, 2004

To Whom It May Concern:

This letter is to inform the reader about the modifications performed on the Masimo SET Radical Pulse Oximeter to be used in an NICHD Neonatal Network trial entitled " The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) Trial". This study, lead by Dr. Neil Finer (UCSD) will evaluate two oxygenation ranges on infants immediately after birth and during their hospital stay. In order to mask the oxygenation ranges from the clinicians in the study, these researchers have asked Masimo Corporation to slightly alter the reading displayed on the Masimo Radical pulse oximeter between the 84% to 96% range. One group of pulse oximeters will read approximately 3% higher than the actual number while the other group of pulse oximeters will read approximately 3% low in this range. The researchers have required that the actual number be displayed below 85% and above 95%. The alarm will sound at 84% and 96%.

Masimo has performed validation tests on this software and found it works per the researchers' request. In addition, all alarms and error messages are still intact and active.

Masimo was willing to mask the pulse oximeters per the researchers' instructions since the intended ranges used in the study are in common use in Neonatal Intensive Care Units (NICUs) across the country. This study is aimed at refining the guidelines as to the best oxygen management range for neonates.

Respectfully,

Michael T. Petterson
Sr. Director, Clinical Research
Masimo Corporation

James Cronin
Vice President, Regulatory Affairs
Masimo Corporation
Irvine, CA

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Stile, Christina (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: RE: Question re: SUPPORT Study
Date: Thursday, May 09, 2013 12:26:00 PM

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Stile, Christina (NIH/NICHD) [E]
Sent: Thursday, May 09, 2013 12:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Stile, Christina (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]
Subject: RE: Question re: SUPPORT Study

thoughts?

(b)(5)

(b)(5)

Best—
Christina Stile, ELS
NICHD, NIH, HHS

From: NICHD Information Resource Center (IRC)
Sent: Thursday, May 09, 2013 11:52 AM
To: Stile, Christina (NIH/NICHD) [E]
Subject: FW: Question re: SUPPORT Study

From: (b)(6) [mailto:(b)(6)@gmail.com]
Sent: Thursday, May 09, 2013 11:24 AM
To: NICHD Information Resource Center (IRC)
Subject: Fwd: Question re: SUPPORT Study

Hello,

I am trying to determine if my twins were enrolled in the following study in 2008:

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

I do not remember if I consented to the study, but they meet all of the study requirements and were born at (b)(6)

Thank you,
(b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Stile, Christina (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]
Subject: RE: Question re: SUPPORT Study
Date: Thursday, May 09, 2013 12:13:00 PM

Sure

- Send something like:

(b)(5)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Stile, Christina (NIH/NICHD) [E]
Sent: Thursday, May 09, 2013 12:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]
Subject: RE: Question re: SUPPORT Study

ok.

could you review my response before i send out?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 09, 2013 12:10 PM
To: Stile, Christina (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]
Subject: RE: Question re: SUPPORT Study

I would suggest that this (b)(5) The DCC does not have patient identifiable information.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH

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higginsr@mail.nih.gov

From: Stile, Christina (NIH/NICHD) [E]
Sent: Thursday, May 09, 2013 12:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Blansfield, Earl (NIH/NICHD) [E]; Stile, Christina (NIH/NICHD) [E]
Subject: FW: Question re: SUPPORT Study

hi rose—

we received this inquiry in the IRC emailbox. is there someone at the DCC that i should contact about this?

please advise. thanks—c

From: NICHD Information Resource Center (IRC)
Sent: Thursday, May 09, 2013 11:52 AM
To: Stile, Christina (NIH/NICHD) [E]
Subject: FW: Question re: SUPPORT Study

From: (b)(6) @gmail.com]
Sent: Thursday, May 09, 2013 11:24 AM
To: NICHD Information Resource Center (IRC)
Subject: Fwd: Question re: SUPPORT Study

Hello,

I am trying to determine if my twins were enrolled in the following study in 2008:

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

I do not remember if I consented to the study, but they meet all of the study requirements and were born at (b)(6)

Thank you,
(b)(6)

From: Devaskar, Uday
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms
Date: Wednesday, May 08, 2013 3:22:12 PM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 02, 2013 7:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Garg, Meena; Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Devaskar, Uday; Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: REquest for GDB, SUPPORT and FU forms

Hi-

Jack Sinclair is interested in exploring use of the SUPPORT database to develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD.
See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.
Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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From: Luc Brion
To: doctorlevan@gmail.com; Wrage, Lisa Ann; Gantz, Marie; Myra Wyckoff; Pablo Sanchez; Roy Heyne; Mambarambath Jaleel; Wally Carlo, M.D.; nfiner@ucsd.edu; Das, Abhik; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion
Subject: Revised Jackie LeVan"s protocol and manuscript on Changes associated with SUPPORT Trial
Date: Wednesday, May 08, 2013 5:51:22 AM
Attachments: Revised Jackie LeVan Protocol 05-07-13.docx
Jackie Manuscript NRN 050713 LPB.doc

Thank you all for your collaboration with Jackie's study on Changes Associated with SUPPORT.

I attach the revised protocol, as well as the manuscript, which was written for Pediatrics.

The manuscript only includes part of the protocol, and corresponds to data presented at the PAS poster.

Could you please send me your suggestions and comments.

Rose: could you please let me know if I need to submit this to anyone else.

Best regards and thank you for your collaboration,

Luc

Luc P. Brion, MD
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Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

From: Luc Brion
To: Das, Abhik; Gantz, Marie
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie"s study
Date: Wednesday, May 08, 2013 5:23:02 AM

Thanks, Abhik

Luc

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, May 07, 2013 2:16 PM
To: Gantz, Marie; Luc Brion
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Agree; we can just acknowledge the limitations in the discussion.

Thanks

Abhik

From: Gantz, Marie
Sent: Tuesday, May 07, 2013 1:17 PM
To: 'Luc Brion'
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Luc,

That would be the most conservative way to go, but it might be overly conservative for this type of study. I would lean toward considering these analyses to be exploratory, with p values presented for informational purposes (as currently stated in the protocol). Being more rigorous than that by pre-

specifying a conservative cut-off for the p values seems unnecessary to me.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, May 06, 2013 4:46 PM
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: Re: Question about Jackie's study

Marie
Thanks a lot for you feedback.
One more question: Should we adjust the level of significance to 0.0125 for the primary outcomes because we have 4 different primary outcomes?
Luc

Sent from my iPhone

On May 6, 2013, at 3:53 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

> I think the edits to the protocol look good. Thanks, Luc.
>
> Marie
>
> Marie Gantz, Ph.D.
> Senior Research Statistician
> RTI International
> mgantz@rti.org
> 919-597-5110
>
> ---
>
> **From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
> **Sent:** Friday, May 03, 2013 11:13 PM
> **To:** Gantz, Marie; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
> **Subject:** RE: Question about Jackie's study
>
> Marie:
> Thanks a lot
> Here is the revised protocol, with adjustment including all you comments.
>
> Rose:

Could you please let me know how to proceed from this point.
Thanks
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-2835
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, May 03, 2013 7:30 PM
To: Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Luc,

My comments on the proposal are attached. As I mentioned in another email, I have reservations about adding data from during SUPPORT to this analysis. I don't think it will help us answer the question of whether there were secular trends, and it could lead us down a path of making comparisons between infants enrolled and not enrolled in SUPPORT which the SUPPORT subcommittee recently voted against. My concerns are described in more detail in comments in the attached document. However, I am happy to discuss further with the group.

Regarding your question below, I don't see an inherent problem with using gestational age and size for gestational age in the models.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, April 25, 2013 3:07 PM
To: Gantz, Marie; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Marie;
Thanks a lot and thanks for the discussion.
Hopefully this does not impact the results and is thus not important.
However, if it turns out it is a problem with the data, could we use instead gestational age and size for gestational age (e.g., z score) as was proposed in the protocol?
Luc

Luc P. Brion, MD
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luc.brion@utsouthwestern.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, April 25, 2013 2:02 PM
To: Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Cc: Gantz, Marie
Subject: RE: Question about Jackie's study

Luc,

I apologize for the delayed response. This week got away from me, but I would be happy to send my thoughts on looking at trends over time next week when I should have more time to think about it.

On the issue of colinearity between GA and BW, although the two are correlated, we can assess whether that is causing a problem in the model by comparing the estimated effect of covariates in models that include one or both variables. When the sample size is large, it is not necessarily a problem to include both in the model, and by doing so you use more of the available information in the data (as opposed to using SGA). I would also caution that the combination of variables you select can lead to interpretability issues. For example, if BW and SGA (but not GA) are included in a model, then SGA can appear protective because, controlling for BW, the better-off babies are those with higher GA (thus, for a given BW, more likely to be SGA).

I will follow up with you again next week as I am out of the office tomorrow.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 2:44 PM
To: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie; (b)(6) @gmail.com; 'nfiner@ucsd.edu'; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Wally et al:

Thanks for your email.

I agree with you 100%: we do not consider any pre-specified analyses. All these analyses had been pre-specified in the original protocol.
Lisa, Jackie and I had selected for the poster a set of data from the protocol, which we thought would be the most important for PAS.
The only changes in the protocol I submitted yesterday were those proposed by Lisa, Abhik and Marie during the preparation of the poster, and which have already been incorporated in the results in the poster.

The first analysis in my email today would allow to avoid collinearity between GA and birth weight in all multivariate analyses.
The second analysis addresses secular trends, which is a likely criticism of this manuscript.

The other two analyses are clearly exploratory.

We could definitely stop her and prepare the first draft of the manuscript, or run some of the analyses.

Please let me know what you think.

Best regards,

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
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luc.brion@utsouthwestern.edu

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 23, 2013 9:37 AM
To: Luc Brion; Wrage, Lisa Ann; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

We should be careful to add not pre-specified and/or exploratory analyses.

Agree that Marie should be an author.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 9:35 AM
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: Question about Jackie's study

Re: Changes over Time in Therapy and Outcomes Associated with The SUPPORT Trial

I sent you yesterday the proposed revision for the protocol for that study.

May I suggest that Marie Gantz, who contributed so much to the poster, should be listed as a co-author.

I would like everyone's opinion whether additional analyses listed in that protocol, but not yet completed, should be conducted before a first draft of a manuscript.

These analyses include:

1. Using SGA or size for age instead of weight in the multivariate models
2. Building a model incorporating years to assess secular trends; this model could include SUPPORT enrollment as covariate
3. Survey of the 11 participating centers (Page 24)
4. Comparing with another network would be a potential next step; I would not include this in a first manuscript.

Should we have a conference call to review this?

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
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luc.brion@utsouthwestern.edu

UT Southwestern Medical Center

The future of medicine, today.

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 7:40 PM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Embargoed report on SUPPORT study

Understood. It can take a little while for folks to review for proprietary info. We will move forward with all due speed

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 7, 2013, at 7:03 PM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

> Also note that in formal FOIA procedures we cannot release documents/protocols on ongoing trials until we hear back from the PIs that they don't contain proprietary information. We are in the process of hearing back from the PIs.

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 6:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: FW: Embargoed report on SUPPORT study

Thanks rose.

Can you provide me with a two sentence description of why the alarms were set where they were? The table in the public citizen report shows babies were kept in the standard of care range so I am not sure what the big deal is here but I would like to understand the basis for the offset in alarms.

I have a sinking feeling I will be asked about it.

Also, does it strike anyone as odd that we post the documents on a Monday afternoon and they have a report released on Tuesday? Are they just super fast? Astonished to see ruth macklin on this.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, May 07, 2013 6:07 PM
To: Rowe, Mona (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: FW: Embargoed report on SUPPORT study
Importance: High

See the attachment –

I am happy to do whatever to dispel this incorrect information being release to the press

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, May 07, 2013 6:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: FW: Embargoed report on SUPPORT study

Hi Rose.

Just in case you have not received this.

Wally

-------- Original Message --------
Subject: FW: Embargoed report on SUPPORT study
From: James Bakken <jimb@uab.edu>

To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
CC:

Wally,

Good afternoon. Tom Burton with the WSJ sent the attached to Dr. Ed Bell and me (Public Citizen is releasing the attached letter tomorrow morning). He is not running a story but is interested in comment re: the point in the letter about oximeter readings (his comment: "I don't think we're going to do a story about this latest letter from Public Citizen, but I would still appreciate the chance to hear your perspective: Did false oximeter readings in any way change the way doctors took care of these infants?). Ideally, Ed at Iowa will comment. I think he and his PIO are going to discuss the opportunity. Can you call me (205-934-3887) when you have had a chance to review this letter and explain the oximeters to me in this context so I am sure I understand the issue? UAB will likely not comment due to pending litigation.

Jim Bakken | Media Relations

Office of Public Relations and Marketing

UAB | The University of Alabama at Birmingham

o: 205.934.3887 | m: (b)(6)
uab.edu/news | facebook.com/UAB.edu
Knowledge that will change your world

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 7:14 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]
Subject: FW: SUPPORT - the saga continues

Importance: High

Alan/Pat,,
Have alerted hhs so they are not surprised about newest public citizen attack.

(b)(5)

Sadly, ohrp letter will (b)(5)

kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 6:57 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]
Subject: SUPPORT - the saga continues
Importance: High

Hi,

Here is the latest from Public Citizen though not yet sent apparently. We understand (b)(5)
(b)(5)

Kathy

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, May 07, 2013 6:57 PM
To: Hudson, Kathy (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: FW: Embargoed report on SUPPORT study

The oximeter had a software adjustment to read 88-92 percent for both groups. So if an infant was randomized to 91-95, when in the "target range," their oximeter would read 88-92. Same for 85-89, if in the target range, the oximeter would read 88-92. They were in the acceptable ranges. This was done to mask the study.

The PAS meetings occurred over the last 4 days. Dr. Judy Aschner is the chairman of Pediatrics at Einstein and has offered assistance if desired.

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 06:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: FW: Embargoed report on SUPPORT study

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I have (b)(5)

Also, does it strike anyone as (b)(5)
(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, May 07, 2013 6:07 PM
To: Rowe, Mona (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: FW: Embargoed report on SUPPORT study
Importance: High

See the attachment –

I am happy to do whatever to dispel this incorrect information being release to the press

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, May 07, 2013 6:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: FW: Embargoed report on SUPPORT study

Hi Rose.

Just in case you have not received this.

Wally

-------- Original Message --------
Subject: FW: Embargoed report on SUPPORT study
From: James Bakken <jimb@uab.edu>
To: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
CC:

Wally,

Good afternoon. Tom Burton with the WSJ sent the attached to Dr. Ed Bell and me (Public Citizen is releasing the attached letter tomorrow morning). He is not running a story but is interested in comment re: the point in the letter about oximeter readings (his comment: "I don't think we're going to do a story about this latest letter from Public Citizen, but I would still appreciate the chance to hear your perspective: Did false oximeter readings in any way change the way doctors took care of these infants?). Ideally, Ed at Iowa will comment. I think he and his PIO are going to discuss the opportunity. Can you call me (205-934-3887) when you have had a chance to review this letter and explain the oximeters to me in this context so I am sure I understand the issue? UAB will likely not comment due to pending litigation.

Jim Bakken | Media Relations

Office of Public Relations and Marketing

UAB | The University of Alabama at Birmingham

o: 205.934.3887 | m: (b)(6)
uab.edu/news | facebook.com/UAB.edu
Knowledge that will change your world

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, May 07, 2013 3:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: SUPPORT study
Attachments: 05 07 13 SUPPORT clarificationAG.rdh.docx; Cole Pedaitrics editorial 2003.pdf

Hi
I added my comments to Alan's. I have also included the Cole editorial that is quoted in the latest draft. Clearly, the data at the time of the study showed decreased ROP and no mortality signal. I have appended another quote from this editorial into the document. This editorial was written in support of doing these studies. Also, I had sent two of the consent forms (BOOST II) and neither mentioned death in the risks. I am trying to get the other two consent forms.
I believe that (b)(5)

Thanks for all the help!!
Rose

Rosemary D. Higgins, MD
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 2:09 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT study

I have asked OSP and steph for comments so let's wait on them before we respond.
Someone in (b)(5) Caya's comment about this sentence suggests (b)(5)
(b)(5)

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, May 07, 2013 1:35 PM
To: Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT study

I think (b)(5) After quick read, my comments on a couple of specific points are on the attached.

Alan

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 1:15 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT study

FYI, I've only scanned...

From: Palm, Andrea (HHS/IOS)
Sent: Tuesday, May 07, 2013 1:06 PM
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Subject: SUPPORT study

Howard and Francis,

Thanks again so much for your efforts on this. The document clearly demonstrates how much progress and work you and your teams have done. Thank you.

The attached reflects line edits from the folks cc-ed here. In addition, we have three comments that are significant from our perspective.

(b)(5)

Once you've had a chance to look at this, we would welcome your collective thoughts on the most efficient next steps to bring this to closure.

Thanks again,
Andrea

Page 1591 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1592 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1593 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1594 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

PEDIATRICS®

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Resolving Our Uncertainty About Oxygen Therapy

Cynthia H. Cole, Kenneth W. Wright, William Tarnow-Mordi and Dale L. Phelps

Pediatrics 2003;112;1415

were symptom-free for at least 72 hours before the onset of chronic respiratory symptoms. They referenced Wilson and Mikity's report but did not attribute these cases to WMS, although the description is typical. In the report of the National Institute of Child Health and Development Workshop on BPD held in June 2000, Jobe and Bancalari[7] referred to the change in the pathology of the lungs seen in BPD as smaller, and more immature infants have come to constitute the majority of infants who die of BPD. The most recent references in the January 2003 issue of the *Journal of Perinatology*[8,9] are case reports involving infants with WMS. The new BPD, described by Jobe[10] in 1999 as occurring in immature infants who do not have much lung disease soon after birth, fits the clinical picture of WMS. Jobe attributes the new BPD to an aberration of lung development, an inhibition of alveolar and vascular development. I believe that the new BPD and WMS are one and the same. As improvements have taken place in the care of women in preterm labor, in surfactant administration and assisted ventilation, classical BPD, a result of injury to the immature lung, has become less common. Chronic lung disease in the premature infant is increasingly likely to be attributable to the response of the immature lung to early air breathing rather than damage from barotrauma or oxygen toxicity. Separating the classification of BPD by cause is important in improving our understanding of the mechanisms involved and the development of potential remedies. The "new" BPD is not so new, having been reported in the 1960s as WMS. The intriguing question that remains is why WMS appears in some infants but not others of presumably the same maturity at birth.

JOAN E. HODGMAN, MD
Department of Pediatrics
Keck School of Medicine
University of Southern California
Los Angeles, CA 90033

REFERENCES

1. Wilson MG, Mikity VG. A new form of respiratory disease in premature infants. *J Dis Child*. 1969;99:489–499
2. Hodgman JE, Mikity VG, Tatter D, Cleland RS. Chronic respiratory distress in the premature infant: Wilson-Mikity syndrome. *Pediatrics*. 1969;44:179–195
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4. Coalson JJ, Winter VT, Siler-Khodr T, Yoder BA. Neonatal chronic lung disease in extremely immature baboons. *Am J Respir Crit Care Med*. 1999;160:1333–1346
5. Weinstein MR, Oh W. Oxygen consumption in infants with bronchopulmonary dysplasia. *J Pediatr*. 1981;99:958–961
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7. Jobe AH, Bancalari E. NICHD/NHL Workshop summary: bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163:1723–1729
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9. Hoffman D, Brown GD, Wirth FH, Gebert BS, Bailey CL, Anday EK. Urinary tract infection with Trichomonas vaginalis in a premature newborn infant and the development of chronic lung disease. *J Perinatol*. 2003;23:59–61
10. Jobe AH. The new BPD: an arrest of lung development. *Pediatr Res*. 1999;66:641–643

Resolving Our Uncertainty About Oxygen Therapy

ABBREVIATIONS. ROP, retinopathy of prematurity; Pao_2, blood oxygen; tco_2, transcutaneous oxygen; Spo_2, oxygen saturation; RLF, retrolental fibroplasia.

Win Tin[1] eloquently articulated in his editorial "Oxygen Therapy: 50 Years of Uncertainty" that neonatal care providers do not understand how best to use oxygen in the most vulnerable premature infants despite >50 years of oxygen therapy in neonatal medicine.[1] We do not understand optimal oxygenation management in extremely low gestational age neonates (<28 weeks' gestation), because we do not know what are safe and effective upper and lower limits of oxygen levels or saturation ranges in both the early and later neonatal courses.[1–7] There has been no implementation of the most powerful tool in clinical research, the randomized, controlled trial, to resolve the uncertainty since the early clinical trials in the 1950s.[8–15] No randomized control trial has clarified the relation between retinopathy of prematurity (ROP) and blood oxygen (Pao_2), transcutaneous oxygen (tco_2), or oxygen saturation (Spo_2) levels. Furthermore, the effects of "higher" versus "lower" oxygen levels or saturation ranges on ROP, growth, brain, lung, and other organ systems have not been studied with respect to gestational age, time of onset or duration of specified oxygen level or saturation range, or method of oxygen termination. Because of the lack of definitive evidence on which to base policy, neonatal care providers differ widely, with no consensus in their policies, practices, and strong beliefs regarding oxygen management in both the early and later neonatal courses of premature infants.[2,16–20] Thus, the study of oxygen therapy in the neonatal population at highest risk for oxygen-related morbidities is an extremely important and urgent issue. We strongly agree with Tin[1,2,16] and others[18–22] that an adequately powered, large, randomized, controlled trial must be conducted to resolve the uncertainty and determine the impact of different ranges of oxygen levels or saturations, initiated early in the neonatal course, on ROP and other important outcomes such as mortality, long-term neurodevelopmental outcome, bronchopulmonary dysplasia, and growth. One of the most compelling arguments for a randomized trial is that continued treatment of millions of premature infants in ignorance of what is safe and effective oxygenation is not an option. The objectives of this commentary are to advocate for a definitive

Received for publication Jan 13, 2003; accepted May 28, 2003.
This editorial is dedicated to the memory of Dr. Douglas K. Richardson, whose life was a testament to the ideal of mutually supportive collaboration.
Address correspondence to Cynthia H. Cole, MD, MPH, Division of Newborn Medicine, Floating Hospital for Children, Tufts-New England Medical Center, 750 Washington St, Boston, MA 02111. E-mail: ccole@tufts-nemc.org
PEDIATRICS (ISSN 0031 4005).

clinical trial, summarize the background and rationale for the trial, and emphasize important methodological issues that must be considered in such a trial.

BACKGROUND

The unrestricted use of oxygen proceeded largely without question until clinical trials published in the 1950s established an association between the use of unrestricted, prolonged oxygen exposure and retrolental fibroplasia (or RLF, as ROP was known initially).[8–15] Meta-analysis of 3 early, randomized trials compared the effect of restricted versus unrestricted oxygen administration on RLF. This analysis revealed a significant reduction, but not complete elimination, in the occurrence of any RLF (event rate ratio: 0.34; 95% confidence interval: 0.25, 0.46) and of severe RLF (event rate ratio: 0.38; 95% confidence interval: 0.17, 0.85) in the restricted oxygen group.[23] Two trials found a statistically insignificant increased risk of mortality.[10,11,23] In a separate meta-analysis of the effects of lower versus higher oxygen concentrations on multiple outcomes in preterm infants during 5 early trials (1951–1969), Askie and Henderson-Smart[24] found that the restriction of oxygen reduced the incidence and severity of RLF without increasing mortality. They calculated that one would only need to treat 3 infants with restricted oxygen to prevent one infant from having an adverse outcome of death or RLF. The drastic curtailment of oxygen administration in the 1950s, subsequent to the clinical trials, was associated with a dramatic reduction in retinopathy. The oxygen curtailment was also associated with a concomitant increase in death and cerebral palsy.[24–27]

These events in the 1950s provide important lessons in medical history regarding ROP. In these early clinical trials, some premature infants developed retinopathy in the restricted oxygen group, and the majority of premature infants in the unrestricted, prolonged oxygen group never developed RLF. One lesson, even from 50 years ago, is that oxygen is an important, but not a sufficient, single cause of ROP. Events of the 1950s also illustrate in hindsight the importance of conducting adequately powered, large, masked, randomized studies with long-term outcomes.

Over the course of the 1970s and 1980s, technical development of means to assess an infant's oxygenation status, either intermittently or continuously, evolved. This included measuring oxygen tension in arterial blood gases or by tco_2 monitoring and estimation of hemoglobin oxygenation saturation by pulse oximetry.[23] One trial demonstrated no benefit of using intermittent arterial blood gases by umbilical arterial catheters in reducing ROP.[13] Another study that evaluated continuous versus intermittent tco_2 monitoring showed that continuous tco_2 monitoring did not reduce ROP.[28] A later analysis of the data from that study suggested that ROP occurred more often when tco_2 monitoring was >80 mm Hg (10.7 pK_a) in the first 4 weeks of life.[29]

Among 5 recent observational studies (2 published articles and 3 abstracts), 4 provide evidence of less severe ROP, and 3 provide evidence of less chronic lung disease in nurseries that had policies of lower Spo_2 ranges compared with higher Spo_2 ranges.[16,18,19,30,31] The Spo_2 ranges evaluated differed among the 5 studies. Two of the 5 cohort studies suggest that a lower versus higher Spo_2 range (Spo_2 ~80 <90% vs >90%) early in the neonatal course can reduce the induction of severe ROP without increasing mortality or cerebral palsy.[16,30] Sun[18] analyzed data from the Vermont-Oxford Network of infants with birth weights 500 to 1000 g to explore possible association between choice of target Spo_2 levels and rate of chronic lung disease, severe ROP, and ROP surgery. Sun found significantly less chronic lung disease, less stage 3 ROP, less need for ROP surgery, and slightly less mortality (although not statistically significantly different) among nurseries that maintained maximum $Spo_2 \leq 95\%$ vs >95%.[18] A recent national survey of pulse oximetry before and after 2 weeks of life found significantly less retinal ablative surgery in neonatal intensive care units with policies of maximum $Spo_2 \leq 98\%$ vs >98% in the first 2 weeks of life. There was also less stage 3 ROP and less need for retinal ablative surgery in nurseries that had maximum $Spo_2 \leq 92\%$ vs >92% after the first 2 weeks of life.[19] Only one observational study suggests that a lower Spo_2 range is associated with increased ROP greater than stage 2, but no increase in surgically treated ROP.[31] These cohort studies illustrate the ongoing uncertainty about oxygen therapy in premature infants and underscore the importance of conducting a randomized, control trial regarding different Spo_2 ranges. The findings of these cohort studies justify testing the hypothesis that a strategy of maintaining a functional Spo_2 level in a "lower" versus "higher" range early in the course of extremely low gestational age neonates reduces the incidence of severe ROP without increasing important adverse neonatal outcomes. We plan to test this hypothesis through an international, multicenter, masked, clinical trial in which extremely low gestational age neonates (<28 weeks' gestation) will be randomly assigned to 1 of 2 scientifically and clinically acceptable pulse oximetry saturation ranges such as 85% to 89% vs 91% to 95% (functional saturation). Acceptability of these ranges would be confirmed additionally through surveys. Randomly assigned intervention would occur shortly after birth and continue through the first several weeks. Tin and Wariyar[2] expanded the background and clearly articulated the justification for such a trial in a separate recent publication.

METHODOLOGICAL IMPLICATIONS FOR A TRIAL OF OXYGEN THERAPY

Sufficiently Powered, Randomized Trial

This important research hypothesis can be tested only by using a sufficiently powered, randomized trial that ensures long-term follow-up. The randomized trial is widely accepted as the best way to minimize systematic bias. Too often, however, unreliable or incorrect answers are generated by randomized trials that have insufficient power to detect clinically

important, small to moderate effects.[32] Sufficient power to detect clinically important, small to moderate effects, in relatively uncommon outcomes such as severe ROP and death, beyond a reasonable doubt may require surprisingly large numbers. Two examples illustrate this. Oral aspirin therapy in myocardial infarction was not widely accepted until after the Second International Study of Infarct Survival in 1988, which enrolled >17 000 patients[33] and confirmed a highly significant 23% reduction in mortality. This finding occurred 14 years after the first trial and after 6 trials showed statistically insignificant reductions (between 10% and 30%) in mortality.[34] It took 20 years, 15 trials, and >3500 infants before it became accepted that antenatal steroids reduced respiratory distress syndrome and intraventricular hemorrhage by 50% and neonatal mortality by 40%.[35,36] Medical research, and specifically neonatal research, needs to find ways of greatly increasing the size of randomized studies. Otherwise moderate but worthwhile benefits may be missed.[37]

Several hundred patients (15–25 centers) may be sufficient to demonstrate important differences in severe ROP. However, a much larger sample (and many more collaborators) will be needed to exclude smaller, important differences in outcomes such as mortality and disability to adequately address real concerns about the safety of lower oxygen tensions. For example, a 5% difference in an outcome of death or cerebral palsy is "small" but would have major implications for public health. Preliminary calculations suggest that the trial may require a sample size between 2000 and 4000 extremely low gestational age infants (born at <28 weeks' gestation) to answer these important questions. Participation of centers that undertake long-term follow-up in >90% of their survivors will be necessary.

Thus, the most expedient, ethical, scientifically rigorous way to resolve the uncertainty of oxygen therapy in extremely low gestational age neonates is to conduct a large, multicenter, randomized, masked trial. International collaboration will certainly be needed to ensure timely recruitment of sufficient numbers of extremely premature infants. Furthermore, international collaboration will permit more robust generalizability of the results. Any outcome is more likely to gain broader clinical acceptance, maximizing the benefit to be derived from what is inevitably going to be a major investment of research money. It is unlikely that funding agencies would repeatedly fund trials of the necessary magnitude. Therefore, if it is to be definitive, it must be rigorous and as complete as possible the first time.

Intervention

The intervention will be different pulse oximetry targets such as 85% to 89% vs 91% to 95%. Masking of oximeters, as was done for the Australian Benefits of Oxygen Saturation Targeting trial,[7] is essential to minimize co-intervention and contamination by bias of neonatal care providers. Masking of the pulse oximeters can be accomplished by offsetting the Spo_2 readings by ±3% such that each study group (85–89% vs 91–95%) displays the same Spo_2 range of 88% to 92%. Actual Spo_2 values would appear for Spo_2 <85% and >95%. Establishment and maintenance of equipoise throughout the intervention and assessments are imperative, because we do not yet know if potential clinically important reductions in retinopathy may offset increases in other potentially competing outcomes such as mortality or neurodevelopmental/neurosensory disability.

The trial will face at least 1 challenge in this regard. Some neonatal units regard Spo_2 >90% as mandatory. Accepting uncertainty about this may be difficult. However, there are cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy.[16,30] Creating an international climate of equipoise could be enhanced by surveys[17–19] of potential study centers to identify local target ranges and establish current limits of collective uncertainty. The trial should compare target ranges for Spo_2 within those limits of acceptable uncertainty.

Outcomes

It is essential, both ethically and scientifically, that the trial carefully select and define meaningful outcomes of neonatal intensive care related to oxygen deficit or toxicity. These outcomes include severe ROP, blindness, bronchopulmonary dysplasia, growth, death, and different types of major neurodevelopmental or neurosensory impairment beyond infancy.

Data Safety Monitoring Committee and Plan

It is also essential, both ethically and scientifically, to have an external monitoring committee to ensure that if major differences between the groups with respect to outcomes such as death or severe ROP are detected, they will be detected during the recruitment phase. Appropriate decisions regarding study termination or continuation can be achieved if stringent stopping rules for the Data Monitoring and Safety Committee are based on evidence beyond reasonable doubt of net clinical benefit or harm or futility of finding a difference before recommending trial termination.[37] Evidence of net benefit or harm from one outcome should be considered in the context of other major outcomes. For example, it would be inappropriate to terminate recruitment because of a 3% reduction in severe ROP in the lower oxygen group before the trial had accumulated sufficient power to exclude a 6% increase in mortality or severe neurodevelopmental impairment in the same group. In this case, if the trial were terminated prematurely and lower oxygen became the clinical standard, for every infant whose sight was saved, 2 would die or survive with major disability.

Pragmatic Design and Data Collection

Successful conduct of a much larger-scale trial requires that the design of the trial be as simple and pragmatic as possible to optimize recruitment and maximize the quality of data. Collection of information only on variables related to the major outcomes

of the trial should enable centers to participate enthusiastically without undue burden. Information on ROP, duration of oxygen therapy, survival, neurodevelopmental, neurosensory, and growth status should be recorded prospectively for this trial. Several recent studies have demonstrated that large-scale recruitment[38–42] and follow-up[39,43] in prospective perinatal studies is feasible. The wisdom of collecting only the relevant, necessary data are reflected in the following comment by Peto and Baigent:[32]

> Collecting less information may mean bigger numbers and hence better science: many trials still collect ten or a hundred times too much information per patient, often at the behest of study sponsors or their committees. Requirements for large amounts of defensive documentation imposed on trials by well intentioned guidelines . . . may, paradoxically, substantially reduce the reliability with which therapeutic questions are answered, if their indirect effect is to make randomized trials smaller or even to prevent them starting.

Educational Program

A trial acknowledging that we don't understand how to provide optimum oxygenation requires extensive education and dialogue with all staff caring for eligible infants. Their insight and support will be crucial. Therefore, one critical element in preparing for this trial is to develop a comprehensive education package that explains the background and rationale of the study that can be used in many national settings.

Trial Planning

The planning for such a trial is in progress. The proposed trial, Pulse Oximetry Saturation Trial for Prevention of ROP (POST ROP), will be adequately powered to reliably detect small to moderate, clinically important differences in severe ROP, chronic lung disease, and differences in mortality, adverse neurodevelopmental and neurosensory (visual/auditory) outcome, and growth. The POST ROP Planning Study Group evolved from collective individual and group endeavors, meetings, and discussions of ophthalmologists and neonatologists over the past year. The POST ROP Planning Group welcomes contact from centers that may be interested in participating in a large trial of oxygen therapy. Without whole-hearted international collaboration, we face many more years of uncertainty about one of the most basic priorities of neonatal care—providing an appropriate concentration of oxygen for our patients.

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Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity (POST ROP) Planning Study Group

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ACKNOWLEDGMENTS

We thank the following members of the Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity Study Planning Group for review and critique of this commentary: Waldemar Carlo, John Flynn, William Good, Jeffrey Horbar, Alan Jobe, Earl Palmer, Betty Vohr, and David Wallace (United States); Lisa Askie, Anne Cust, Peter Davis, David Henderson-Smart, Jane Lloyd, Colin Morley, and John Simes (Australia); Edmund Hey and Win Tin (United Kingdom); Christian Poets (Germany); and Keith J. Barrington, Barbara Schmidt, and Jack Sinclair (Canada).

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Zinc, Low Birth Weight, and Breastfeeding

ABBREVIATION. SGA, small for gestational age.

The article by Sur et al[1] in this issue further emphasizes the value of both breastfeeding and an adequate zinc intake for infants. The notable contribution of zinc deficiency in infancy and early childhood to stunting[2] and infectious disease morbidity[3] and mortality,[4] especially from diarrhea and pneumonia, is now well-documented in developing countries.

In the study by Sur et al, zinc supplementation of low birth weight infants for the first year of life was associated with improved growth and reduced diarrheal morbidity. In another study from India, zinc supplementation of small for gestational age (SGA) infants from ~1 to 10 months postnatal age was associated with a two-thirds reduction in mortality.[5] Most low birth weight infants in developing countries are SGA. Neonatal reserves of zinc in SGA infants are lower than those of appropriate for gestational age infants, even on a body weight basis,[6] and these supplementation studies support a particular vulnerability to zinc deficiency in this group. Thus special attention to an adequate postnatal zinc intake is indicated for the SGA infant.

The independent protective effect of exclusive breastfeeding noted in this study raises the question of whether the diarrhea associated with introduction of potentially contaminated complementary foods at 4 months caused increased zinc losses and whether, had exclusive breastfeeding been continued longer, the onset of zinc deficiency would have been delayed. Alternatively, zinc deficiency may have been developing by 4 months, resulting in increased susceptibility to diarrhea. This study does not answer these questions but illustrates well the challenge of defining optimal timing of introduction of complementary foods, especially in vulnerable infants in vulnerable conditions. There is little doubt that even the term, appropriate for gestational age, older breastfed infant is susceptible to zinc deficiency after ~6 months when milk zinc concentrations are very low relative to requirements.[7,8] The availability of complementary foods of favorable bioavailability, especially animal products, is critical to attaining adequate zinc intake. In our experience, poor appetite and slow growth attributable to zinc deficiency occur in North America in older breastfed infants if complementary foods with bioavailable zinc, such as meats, are not consumed. The studies by Sur et al and others are reminders of both the importance and complexity of meeting the needs of this micronutri-

Received for publication Aug 1, 2003; accepted Aug 1, 2003.
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PEDIATRICS (ISSN 0031 4005).

Resolving Our Uncertainty About Oxygen Therapy

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Pediatrics 2003;112;1415

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

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From: Luc Brion
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie"s study
Date: Tuesday, May 07, 2013 3:17:00 PM

Thanks for your feedback.
I will send the protocol and manuscript to all authors
Best regards,
Luc

From: Gantz, Marie [mgantz@rti.org]
Sent: Tuesday, May 07, 2013 12:16 PM
To: Luc Brion
Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Luc,

That would be the most conservative way to go, but it might be overly conservative for this type of study. I would lean toward considering these analyses to be exploratory, with p values presented for informational purposes (as currently stated in the protocol). Being more rigorous than that by pre-specifying a conservative cut-off for the p values seems unnecessary to me.

Marie

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, May 06, 2013 4:46 PM
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Cc: Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: Re: Question about Jackie's study

Marie
Thanks a lot for you feedback.
One more question: Should we adjust the level of significance to 0.0125 for the primary outcomes because we have 4 different primary outcomes?
Luc

Sent from my iPhone

On May 6, 2013, at 3:53 PM, "Gantz, Marie" <mgantz@rti.org> wrote:

I think the edits to the protocol look good. Thanks, Luc.

Marie

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
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To: Gantz, Marie; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Marie:
Thanks a lot
Here is the revised protocol, with adjustment including all you comments.

Rose:
Could you please let me know how to proceed from this point.
Thanks
Luc

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Subject: RE: Question about Jackie's study

Luc,

My comments on the proposal are attached. As I mentioned in another email, I have reservations about adding data from during SUPPORT to this analysis. I don't think it will help us answer the question of whether there were secular trends, and it could lead us down a path of making comparisons between infants enrolled and not enrolled in SUPPORT which the SUPPORT subcommittee recently voted against. My concerns are described in more detail in comments in the attached document. However, I am happy to discuss further with the group.

Regarding your question below, I don't see an inherent problem with using gestational age and size for gestational age in the models.

Marie

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Subject: RE: Question about Jackie's study

Marie;
Thanks a lot and thanks for the discussion.
Hopefully this does not impact the results and is thus not important.
However, if it turns out it is a problem with the data, could we use instead gestational age and size for gestational age (e.g., z score) as was proposed in the protocol?
Luc

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To: Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Cc: Gantz, Marie
Subject: RE: Question about Jackie's study

Luc,

I apologize for the delayed response. This week got away from me, but I would be happy to send my thoughts on looking at trends over time next week when I should have more time to think about it.

On the issue of colinearity between GA and BW, although the two are correlated, we can assess whether that is causing a problem in the model by comparing the estimated effect of covariates in models that include one or both variables. When the sample size is large, it is not necessarily a problem to include both in the model, and by doing so you use more of the available information in the data (as opposed to using SGA). I would also caution that the combination of variables you select can lead to interpretability issues. For example, if BW and SGA (but not GA) are included in a model, then SGA can appear protective because, controlling for BW, the better-off babies are those with higher GA (thus, for a given BW, more likely to be SGA).

I will follow up with you again next week as I am out of the office tomorrow.

Marie

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Subject: RE: Question about Jackie's study

Wally et al:

Thanks for your email.

I agree with you 100%: we do not consider any pre-specified analyses. All these analyses had been pre-specified in the original protocol.
Lisa, Jackie and I had selected for the poster a set of data from the protocol, which we thought would be the most important for PAS.
The only changes in the protocol I submitted yesterday were those proposed by Lisa, Abhik and Marie during the preparation of the poster, and which have already been incorporated in the results in the poster.

The first analysis in my email today would allow to avoid collinearity between GA and birth weight in all multivariate analyses.
The second analysis addresses secular trends, which is a likely criticism of this manuscript.
The other two analyses are clearly exploratory.

We could definitely stop her and prepare the first draft of the manuscript, or run some of the analyses.

Please let me know what you think.

Best regards,

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To: Luc Brion; Wrage, Lisa Ann; Gantz, Marie; (b)(6) @gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

We should be careful to add not pre-specified and/or exploratory analyses.

Agree that Marie should be an author.

Wally

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Subject: Question about Jackie's study

Re: Changes over Time in Therapy and Outcomes Associated with The SUPPORT Trial

I sent you yesterday the proposed revision for the protocol for that study.

May I suggest that Marie Gantz, who contributed so much to the poster, should be listed as a co-author.

I would like everyone's opinion whether additional analyses listed in that protocol, but not yet completed, should be conducted before a first draft of a manuscript.

These analyses include:

1. Using SGA or size for age instead of weight in the multivariate models
2. Building a model incorporating years to assess secular trends; this model could include SUPPORT enrollment as covariate
3. Survey of the 11 participating centers (Page 24)
4. Comparing with another network would be a potential next step; I would not include this in a first manuscript.

Should we have a conference call to review this?

Luc

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Blansfield, Earl (NIH/NICHD) [E]

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To: Collins, Francis (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]
Subject: Fwd: Preemie studies - heads up

Fc
I did not include bill. I also (b)(5)
(b)(5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
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Begin forwarded message:

From: "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>
Date: May 5, 2013, 12:54:46 PM EDT
To: "Koh, Howard (HHS/OASH)" <Howard.Koh@hhs.gov>, "Menikoff, Jerry (HHS/OASH)" <Jerry.Menikoff@hhs.gov>, "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov>, "Palm, Andrea (HHS/IOS)" <Andrea.Palm@hhs.gov>
Cc: "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>, "Devaney, Stephanie (NIH/OD) [E]" <stephanie.devaney@nih.gov>, "Patterson, Amy (NIH/OD) [E]" <PattersA@OD.NIH.GOV>, "Carr, Sarah (NIH/OD) [E]" <CarrS@OD.NIH.GOV>
Subject: Preemie studies - heads up

http://jama.jamanetwork.com/article.aspx?articleid=1684963

Wanted to make sure you were aware that Canadian study analogous to SUPPORT was published online in JAMA this morning. No statistically significant differences in mortality between arms - Alan, please chime in with nuances if needed

Two other SUPPORT - like studies are on deck to be published in NEJM. All of these studies are being presented at the peds meeting going on this weekend. KGS speaking at this meeting Monday.

Consents for these studies will be public as part of publications etc.

Also, on semi related note, information on our newborn research network studies will be sent to public citizen in response to FOIA tomorrow (we are at the deadline) and we will subsequently post on our Webpages.

Too much going on!

Let me know if you have questions.

Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sunday, May 05, 2013 10:04 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: Fw:
Attachments: UK BOOSTII-PIL.pdf; Parent Information and Consent Form V2 240806.doc

See below - I was blind copied on this email- likely to see more in the news given the two presentations just given at the PAS Rosemary D. Higgins Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: William Tarnow-Mordi [mailto:williamtm@med.usyd.edu.au]
Sent: Saturday, May 04, 2013 07:56 AM
To: Hoffman, Jan <hoffman@nytimes.com>
Cc: williamtm@med.usyd.edu.au <williamtm@med.usyd.edu.au>
Subject:

Dear Ms Hoffman

Sorry for the delay in responding. (It was Saturday here in Australia).

Lisa Askie passed me your request for the BOOST II Consent forms and I've spoken to Ben Stenson. I believe you already have the NZ consent form from Brian Darlow.

Here are the Australian and UK parent information and consent forms used in the BOOST II studies. They were also submitted to NEJM and will be shortly be available on the journal's website.

Don't hesitate to get back if there are other details that would be helpful.

William Tarnow-Mordi

on behalf of the

Australian BOOST II Collaborative Group

--
William Tarnow-Mordi
Professor of Neonatal Medicine, Westmead Hospital NHMRC Clinical Trials Centre, University of Sydney, Foundation Director Westmead International Network for Neonatal Education and Research WINNER Centre - working together to win healthy survival.

BOOST - II UK

Benefits Of Oxygen Saturation Targeting

Information Leaflet for Parents

Summary

This is a brief summary of a research study about the amount of oxygen that very premature babies receive. You have been given this leaflet because your baby has been, or may be, delivered more than 12 weeks early and we want to give you the opportunity to think about whether you would like your baby to take part in this study.

Extra oxygen helps premature babies in their first few days or weeks after birth. However, we also know that it is possible to give too much oxygen or too little. We are confident that the amount we currently give is about right, but within the range that we currently use, it is possible that a slightly higher or a slightly lower amount might be better. Our hospital is one of forty centres helping the Medical Research Council to find out which approach is best.

If, after reading this information and discussing the study with the doctors and nurses in the neonatal unit, you decide to let your baby take part we will ask you to sign a consent form. Your baby will then be entered into the study. Your baby will require no extra blood tests or other investigations because they are in the study. We will collect information about your baby's progress in hospital and then we would like to see you both when your baby is [illegible] years old at a clinic appointment. You may be asked [illegible]

Whether or not you decide to let your baby take part in the study is entirely up to you.

If you decide not to take part this will not affect the [illegible] your baby receives.

[illegible] The rest of this leaflet explains [illegible] being in the study. Please read [illegible]

ISRCTN00842661, MREC Number: 06/MRE04/91, Version 3, March 2007

Formal Title: What oxygen saturation level should we target in very premature infants? A randomised controlled trial.

We understand and appreciate that this is a very difficult time for you. You may feel that now is not a good moment to be talking about research. However, we think it is important that you know about a study that this hospital is taking part in for babies born prematurely.

The BOOST-II UK study aims to find out how much extra oxygen we should give premature babies in their first few days or weeks in the neonatal unit. Because we need to give babies extra oxygen from the time they are born you will need to decide whether you wish to take part in this study before your baby is 12 hours old (or 24 hours if your baby was born in another hospital). Before you make this decision, it is important for you to understand why we are doing this research and what it means for your baby.

Please take the time to read the following information carefully so that you can decide whether or not you want your baby to take part. To help you make a decision you feel comfortable with, a doctor or nurse who is familiar with the study will also explain what it involves and will be happy to answer any of your questions.

What is the purpose of the study?

We know that giving premature babies extra oxygen after birth is often necessary for them to survive. We therefore closely monitor the amount of oxygen in the blood in premature babies to see whether they need extra oxygen and if so, how much to give.

The amount of oxygen in the blood is called the "oxygen saturation" and this is measured by special monitors called "oximeters". They measure the oxygen saturation of the blood by using sensors. The sensor rests on the surface of the skin and a light shines onto the skin and from this we can tell how much oxygen is in the baby's blood. An oximeter is already used for all premature babies and it is completely painless. This picture shows a sensor on a baby's foot. A

place.

In most modern neonatal units we aim to keep the oxygen saturation between 85% and 95%, and we believe that this is the safe range for premature babies. However, we are still not sure whether, within this range, we should give slightly more or slightly less oxygen. If we give babies too much oxygen we can cause problems with their health. For example, too much oxygen can damage a premature baby's eyes and, if this is very severe, it can lead to blindness. On the other hand, too little extra oxygen can cause problems with the development of their brain.

In this study we are trying to find out whether keeping the oxygen saturation between 85% and 89% is better, or worse, or no different, than keeping it between 91% and 95%.

How will oxygen levels be measured in the study?

In order to keep the amount of oxygen given to the two groups of babies different, we are using special oximeters in this study. When the baby's oxygen is between 85% and 95% then one group of monitors will read 3% higher than the true oxygen saturation and one group will read 3% lower. The doctors and nurses in the study will be asked to aim to keep each baby in the study between 88% and 92% while they are receiving extra oxygen. If the baby's oxygen saturation is ever above 95% or below 85%, then the true value will be displayed. The doctors and nurses will not know whether the oximeter being used on a baby is reading higher or lower than the reading displayed. Therefore, they will not know the true oxygen saturation of the babies in the study. However, whichever monitor is used, oxygen saturation will be targeted within the range we currently understand to be safe.

Why has my baby been chosen?

Most babies born very early require extra oxygen. We are therefore inviting all parents of babies born prematurely to consider entering this study.

This hospital is one of 40 hospitals in the UK and Ireland taking part in this study and we hope that 1200 babies will take part.

This study is one of five similar studies taking place throughout the world to answer this important question of how much oxygen we should give premature babies. Anonymised information about your baby will be shared with researchers around the world [illegible] aiming to recruit more than 5,000 babies [illegible]

Does my baby have to take part?

You do not have to agree to your baby taking part in this study. If you decide not to take part, your baby will receive usual care and will receive the amount of oxygen the doctors in the neonatal unit currently use. If you do decide that you would like your baby to take part and then change your mind later your baby can be taken out of the study at any time, without having to give a reason. Your decision whether or not to take part will not affect the normal high level of care given in the neonatal unit.

What will happen to my baby if I agree to take part?

If you agree that you would like your baby to take part in this study, your baby will be put into one of two groups. One group will get enough oxygen to try to keep their oxygen saturations at between 85% and 89%. The second group will be given enough oxygen to try to keep their oxygen saturations between 91% and 95%. Both are within the range of values that are routinely used.

Your baby will have a 50/50 chance of being put into either of these groups. It is not possible to know beforehand which group your baby will be in, this will rely on chance (rather like tossing a coin). This makes sure that we test fairly whether one level is better than the other level.

No extra blood tests or injections are necessary, and all the other care that your baby gets will be the same whether you let your baby take part in the study or not.

For babies who go home we would like to send a brief questionnaire (about one page) every four months before their first birthday and every six months before their second birthday. This questionnaire will ask if your baby has had to go back into hospital for any reason, how many days your baby was in hospital and the reason for being re-admitted. It is also very important that we know how they are getting on at around 2 years of age. We will contact all the families in the study close to the baby's second birthday to see how they are. From when a baby in the study goes home until they are two years old, the doctors looking after you will arrange to see your baby as outpatients as part of the routine care for all premature babies. After some of these visits they will let us know how you are getting on and ask you to fill in any questionnaires that are part of the study that are not part of routine care.

We would also like to contact your child's [illegible] to see how your child is [illegible]

ISRCTN00842661, MREC Number: 06/MRE04/91, Version 3, March 2007

that time. Presently we do not have funds to do this but we will keep in touch and let you know whether or not this will happen.

What are the possible side effects of the treatment?

Oxygen is usually required by premature babies and can be life saving. However, as we have said earlier, giving too much oxygen can cause damage to a baby's eyes and lungs. Giving too little oxygen can cause problems with the normal development of the brain.

The two ranges of oxygen saturation that we are looking at in this study are within the range that doctors throughout the world currently use.

Whichever group your baby is in, your baby will be monitored very closely by the hospital staff in the neonatal intensive care unit.

What are the possible disadvantages and benefits of taking part?

There are no real disadvantages for you in taking part in this study, but as part of the study, we will need to collect information about your baby. This information will be about the care your baby received while in the neonatal unit.

What if new information becomes available?

The staff conducting this study will inform you of any new information that becomes available during the course of the study which might make you change your mind about staying in the study.

The doctors looking after your baby may take your baby out of the study at any time, for example if your baby became very ill. They may also choose to give your baby extra oxygen if they feel this is necessary, for example, if your baby needed surgery. Taking part in the study will not stop the staff looking after your baby from doing whatever is necessary to make the best possible care of your baby.

What if something goes wrong?

The chance of anything going wrong as a result of taking part in this study is very small. However, we are required to tell you the following:

If your baby is harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Oxford in respect of any harm caused.

Trial or the NHS in respect of any harm which has resulted from the clinical procedure being undertaken.

Will my taking part in this study be kept confidential?

Because we need to contact you to find out how your baby is at two years of age, we need your name, your address and other contact details. The NHS has a central register (based at the General Register Office) which we will be using to keep in touch with you. This register will let us know if you or your baby leaves the NHS. Your GP will also be told that your baby took part in this study. These details will be kept securely and will only be seen by the study organisers and people from the regulatory authorities eg. from the NHS Trusts' Research and Development Office who ensure that studies such as these are carried out safely. They may also look at your baby's notes to check that the study is being carried out correctly. Information about your baby will not be used for any purpose other than to answer this research question.

What will happen to the results of the research study?

At the end of the study, the results will be analysed and published in an international medical journal. We will send you a summary of the final results of the study. A copy of the full journal article can be requested from the National Perinatal Epidemiology Unit. You and your baby will not be identified in any report or publication about the study.

Who is organising and funding the research?

The study is being run by the National Perinatal Epidemiology Unit at the University of Oxford.

The study is funded by the Medical Research Council.

Who has reviewed the study?

All research that involves NHS patients, staff, information from NHS medical records or uses NHS premises or facilities must be reviewed by a NHS Research Ethics Committee (REC). The [illegible] application does not guarantee that you will not come to [illegible]. However, approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and are balanced against possible benefits, and that you will be given enough information on which to make an informed decision to take part. The [illegible] Centre Research Ethics Committee reviewed this study.

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Thank you for reading this information leaflet. The doctor or nurse who gave you this leaflet will be pleased to discuss the study in more detail and provide further information if this would be helpful. Alternatively, the contact details of the study's Principal Investigator and Study Nurse are provided on this page.

What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Principal Investigator [their name and contact details are on this page], or you may contact the hospital complaints department.

Information is also available on the study website www.npeu.ox.ac.uk/boost

Local contact (enter details below):

BOOST II Study Co-ordinator

NPEU CTU
University of Oxford
Old Road Campus
Headington

Email:

ISRCTN00842661, MREC Number: 06/MRE04/91, Version 3, March 2007

BOOSTII
BENEFITS OF OXYGEN SATURATION TARGETING

INFORMATION FOR PARENTS

Which oxygen level should we use for very premature infants?

We invite you to join an international study of the
Benefits of Oxygen Saturation Targeting (BOOST II)

What is the purpose of the study?

- Doctors and nurses worldwide try to give premature babies enough oxygen to keep blood oxygen saturation between 85% and 95%.
- We now need to find out if the upper or lower part of this range is better.
- Too much or too little oxygen for long periods may harm babies' eyes, lungs and brain, in or out of the study.

What does this study involve?

- Premature babies have oxygen levels (saturation) monitored all the time with a pulse oximeter. This doesn't hurt.



- The study will aim to enroll about 1200 babies in Australia and 5,000 worldwide.
- Babies in the study get an oximeter that reads slightly higher (by 3%) or slightly lower (by 3%) than the actual oxygen saturation. The study oximeter is chosen randomly by a computer (like tossing a coin).
- In babies breathing air, the oximeter may read up to 100%. That is normal.
- In babies on oxygen, we aim to keep saturation as close to 88% - 92% as possible with both types of oximeter.
  - the higher study oximeters read 88% - 92% when actual saturation is 3% lower at 85% - 89%
  - the lower study oximeters read 88% - 92% when actual saturation is 3% higher at 91% - 95%
- Above or below the range of 85 – 95% each oximeter will show the true oxygen saturation.
- The staff do not know which oximeters read higher and which read lower. This is the best way to do the study.
- Your baby keeps the study oximeter until oxygen is not needed or until 36 weeks. If your baby needs oxygen treatment after that, your baby will have a standard nursery oximeter.
- We will record any illnesses in hospital and collect data from the study oximeter.

- If your baby goes to another hospital on oxygen before 36 weeks, the study oximeter will go as well. You do not have to sign another consent form.

- We'll phone you at home at 6, 12 and 18 months to ask how your baby is doing. In the follow up clinic at two years from "term", we will check how your baby sees, hears, talks, walks and thinks. This takes about 2 hours and we will pay your travel expenses if necessary.

What are the possible benefits and risks of taking part in this research?

- Babies in the study will benefit by having oxygen monitored even more closely than normal.

- The main benefit is to test which oxygen level is better for babies in future. This may not directly help your baby.

- Too much oxygen for long periods may harm the eyes, brain cells or lung.

- Too little oxygen for long periods may harm brain cells and contribute to chronic lung disease.

- These risks exist whether your baby is in or out of the study.

Confidentiality

Study information that can identify your child will be confidential. Only staff working in the study and other authorised persons can see your baby's study information or medical records. Study information will be stored at the hospital and the Co-ordinating Centre at The University of Sydney for at least 23 years by law.

Participation is Voluntary

You can decide whether or not to allow your baby to take part in this study. You can withdraw consent at any time without giving a reason. If so, we would ask if we can see your child at two years and keep track of your child through the Meidcare Australia database. You do not have to agree.

If you chose not to take part, it would not affect your baby's treatment or your relationship with the staff. Your baby would have oxygen treatment by the nursery's guidelines.

Contacts or Complaints

You can contact either Dr ..... or Dr..... if you have any questions or concerns arising from taking part in this research. Phone ..... during working hours or ..... (page Dr .....) after hours or by email ..... . The ..... Hospital also has a Consumer Advocate available on .....

In the unlikely event that a child suffers injury as a result of taking part in this study, treatment will be provided by the public health service at no extra cost to you.

Thank you for reading this leaflet. It is for you to keep.

If you join the study, you will also keep a copy of the consent form.

Hospital Letterhead

PARENT CONSENT FORM

Which oxygen level should we use for very premature infants?
The Benefits of Oxygen Saturation Targeting study (BOOST II)

I, ...
Name of Parent/Guardian (please print)

of.....
Address Parent/Guardian (please print)

have read and understood the information for parents on the above named research study and have discussed it with ..... I am aware of the procedures involved in the study, including any inconvenience, risk, discomfort or side effect, and of their implications.

I freely choose to take part in this study and understand that I can withdraw without compromise at any time.

I also understand that the research study is strictly confidential.

I hereby agree for my child ..... to take part in this research study.
Baby's Name (please print)

Signature of parent/guardian:..... Date:____/____/____

Name of witness/ interpreter:..... Signature:.....

Date:____/____/____

Name of person obtaining consent:.....

Signature of person obtaining consent:..... Date:____/____/____

I authorise Medicare Australia to provide updated details of my residential address, as held on Medicare records, to the BOOST II Coordinator, NHMRC Clinical Trials Centre, Locked Bag 77, Camperdown, 2050. This consent remains valid for 5 years from the date this consent is signed.

Medicare number of parent/guardian: _____

Name of parent/guardian:..... Signature:..... Date:____/____/____

Name of witness/ interpreter:..... Signature:..... Date:____/____/____

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Saturday, May 04, 2013 2:16 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: SUPPORT revisited 5-3-2013c nih
Attachments: SUPPORT revisited 5-3-2013c nih.docx

I think I managed to incorporate our comments.
Did I miss anything?
Any additional thoughts?

Page 1624 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1625 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Subject: Re: Support study -
Date: Saturday, May 04, 2013 12:06:30 PM

I agree
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Saturday, May 04, 2013 12:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support study -

What to you think? They do give (b)(5)
(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, May 04, 2013 11:42 AM
To: Maddox, Yvonne (NIH/NICHD) [E]
Subject: Fw: Support study -

FYI
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 04:53 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

Blansfield, Earl (NIH/NICHD) [E]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Saturday, May 04, 2013 11:50 AM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: RE: Support study -

Removing FC –

I agree that (b)(5)
(b)(5)
clarity?

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Saturday, May 04, 2013 11:25 AM
To: Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

All –

I could be happy with the currently proposed letter, were it not for the paragraph:

(b)(5)

Perhaps the (b)(5)
(b)(5)

I agree with Francis that the (b)(5)
(b)(5)

Perhaps (????) something like: (b)(5)
(b)(5)

(b)(5)

Alan

P.S. Simply to make it read more clearly, I would change one other sentence in the letter: (b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 03, 2013 11:14 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Can folks send comments by noon tomorrow?

Most offensive section to me is (b)(5)

(b)(5)

I have shared the draft letter with gary g and jose briggs since they have dogs in this fight.

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

[1] "In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct [what would become known as] the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration." Askie et al., BMC Pediatrics 2011 11:6, at page 3. That collaboration eventually included the SUPPORT study and four similar studies conducted within Canada (COT), the United Kingdom (BOOST-II UK), Australia (BOOST-II), and New Zealand (BOOST NZ). The initial thinking behind this group of studies was "outlined in a [2003] commentary in *Pediatrics*" in which Cole et al., Resolving Our Uncertainty About Oxygen Therapy, *Pediatrics* 2003;112:1415, discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." They also noted a particular challenge in recruiting neonatal units to participate: some units "regard [oxygen levels greater than 90%] as mandatory," and might therefore be unwilling to participate in a study in which one-half the infants would be randomized to levels below 90%. To recruit such units, they suggested using "cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy."

Subsequent official statements regarding SUPPORT and the other four trials, issued prior to the 2010 results from SUPPORT, demonstrate that resolving those "real concerns" about mortality risks at the low oxygen end remained a major issue for these studies. On the official registration system for clinical trials in the U.S., clinicaltrials.gov, the SUPPORT researchers provided a one-sentence description in 2005 saying that it "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants." http://clinicaltrials.gov/archive/NCT00233324/2005_10_04 The description provided on that same database for the Canadian trial in 2008 states that a randomized trial "is urgently needed and long overdue to determine whether oxygen exposure can be reduced safely in extremely preterm infants without increasing the risk of hypoxic death or disability." The United Kingdom protocol noted that "restricting oxygen exposure to minimize [the possibility of severe retinopathy] risks increasing early mortality." http://clinicaltrials.gov/archive/NCT00637169/2008_03_14

See also Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004 (113):394-396 ("For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP blindness, chronic lung disease, and brain damage) was, and remains to this day, unknown"); Tin et al, Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106–F110 ("Because mortality went undocumented in the first of the large trials of oxygen administration, we do not even know if there is a price to be paid for controlling administration strictly enough to minimise the risk of severe retinopathy.") . A Cochrane Collaboration review in 2009 specifically looked at the relationship between oxygen levels and mortality, concluding that the correct range to use was still not yet known. With regard to the most recent studies (from 2001 to 2004) showing no increased mortality at lower oxygen ranges, it noted: "these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide," and that the SUPPORT and other four studies were collecting data to "help resolve this remaining question." Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews 2009(1).

[2] The UAB consent form mentions no risks with regard to the use of lower oxygen levels. In contrast, a 2005 version of the consent form used in the New Zealand BOOST study is reported to have this language: "Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems." Lantos JD. OHRP and Public Citizen are Wrong about Neonatal Research on Oxygen Therapy. Hastings Center Bioethics Forum 2013. And the NeOProM 2011 write-up, mentioned in note 1 above, using only pre-2005 references, describes the risks issue as follows: "There are two opposing concerns. Less inspired oxygen [under 90%] may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development. More inspired oxygen [greater than 90%] may increase severe [retinopathy] and chronic lung disease."

[3] "In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct [what would become known as] the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration." Askie et al., BMC Pediatrics 2011 11:6, at page 3. That collaboration eventually included the SUPPORT study and four similar studies conducted within Canada (COT), the United Kingdom (BOOST-II UK), Australia (BOOST-II), and New Zealand (BOOST NZ). The initial thinking behind this group of studies was "outlined in a [2003] commentary in *Pediatrics*" in which Cole et al., Resolving Our Uncertainty About Oxygen Therapy, *Pediatrics* 2003;112:1415, discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." They also noted a particular challenge in recruiting neonatal units to participate: some units "regard [oxygen levels greater than 90%] as mandatory," and might therefore be unwilling to participate in a study in which one-half the infants would be randomized to levels below 90%. To recruit such units, they suggested using "cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy."

Subsequent official statements regarding SUPPORT and the other four trials, issued prior to the 2010 results from SUPPORT, demonstrate that resolving those "real concerns" about mortality risks at the low oxygen end remained a major issue for these studies. On the official registration system for clinical trials in the U.S., clinicaltrials.gov, the SUPPORT researchers provided a one-sentence description in 2005 saying that it "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants." http://clinicaltrials.gov/archive/NCT00233324/2005_10_04 The description provided on that same database for the Canadian trial in 2008 states that a randomized trial "is urgently needed and long overdue to determine whether oxygen exposure can be reduced safely in extremely preterm infants without increasing the risk of hypoxic death or disability." The United Kingdom protocol noted that "restricting oxygen exposure to minimize [the possibility of severe retinopathy] risks increasing early mortality." http://clinicaltrials.gov/archive/NCT00637169/2008_03_14

See also Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004 (113):394-396 ("For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP blindness, chronic lung disease, and brain damage) was, and remains to this day, unknown"); Tin et al, Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106–F110 ("Because mortality went undocumented in the first of the large trials of oxygen administration, we do not even know if there is a price to be paid for controlling administration strictly enough to minimise the risk of severe retinopathy.") . A Cochrane Collaboration review in 2009 specifically looked at the relationship between oxygen levels and mortality, concluding that the correct range to use was still not yet known. With regard to the most recent studies (from 2001 to 2004) showing no increased mortality at lower oxygen ranges, it noted: "these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide," and that the SUPPORT and other four studies were collecting data to "help resolve this remaining question." Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews 2009(1).

[4] The UAB consent form mentions no risks with regard to the use of lower oxygen levels. In contrast, a 2005 version of the consent form used in the New Zealand BOOST study is reported to have this language: "Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems." Lantos JD. OHRP and Public Citizen are Wrong about Neonatal Research on Oxygen Therapy. Hastings Center Bioethics Forum 2013. And the NeOProM 2011 write-up, mentioned in note 1 above, using only pre-2005 references, describes the risks issue as follows: "There are two opposing concerns. Less inspired oxygen [under 90%] may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development. More inspired oxygen [greater than 90%] may increase severe [retinopathy] and chronic lung disease."

Blansfield, Earl (NIH/NICHD) [E]

From: Collins, Francis (NIH/OD) [E]
Sent: Saturday, May 04, 2013 11:06 AM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: Support study -

I share (b)(5)
(b)(5)

The material on page 3 will be very helpful.

FC

From: Hudson, Kathy (NIH/OD) [E]
Sent: Saturday, May 04, 2013 10:28 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Fwd: Support study -

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

From: "Shurin, Susan (NIH/NHLBI) [E]" <shurinsb@nhlbi.nih.gov>
Date: May 4, 2013, 8:27:02 AM EDT
To: "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>
Cc: "Briggs, Josephine (NIH/NCCAM) [E]" <briggsj@mail.nih.gov>, "Lauer, Michael (NIH/NHLBI) [E]" <lauerm@nhlbi.nih.gov>, "Gibbons, Gary (NIH/NHLBI) [E]" <Gary.Gibbons@nih.gov>
Subject: Re: Support study -

Hi, Kathy,

1. "Lingering concerns" are not (b)(5)
(b)(5)

2. A major study question was the ROP one. It was (b)(5)
(b)(5)

This is still (b)(5)

I hope you can move this in the right direction.

It was a topic of discussion at the joint APS-SPR Council meeting yesterday.

Susan

Sent from my iPhone

On May 3, 2013, at 11:09 PM, "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov> wrote:

> We are in active negotiations with ohrp. This is the most recent overture from ohrp. Alan and I are meeting with them tomorrow. Your comments welcome.
>
> It is good (b)(5)
> (b)(5)
>
> Your thoughts would be most appreciated – preferably before 1 tomorrow since we meet with them at 3.
>
> Thanks so much.
>
> kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

<SUPPORT revisited 5-3-2013c.docx>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Subject: Re: Talking Points.docx
Date: Saturday, May 04, 2013 10:50:32 AM

Talk went fine- thanks for all the help

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, May 03, 2013 06:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: RE: Talking Points.docx

I said Pediatric Trauma and Critical Injury NO, the new branch is Pediatric Trauma and Critical Illness. Sorry.

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, May 03, 2013 6:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: Talking Points.docx

Rose, here are some talking points for the slides for tomorrow. I am sure you have your own content and will say what you feel is appropriate. I did want to share some of my thoughts with you however. They told me that I could go into the Slide Show as late as tomorrow morning and make any changes we want. I do think the talk is probably too long, so you might want to get rid of some of the slides. Thanks for doing this, I wish could be there. There are several receptions that I would have wanted to attend also, so that I could see some of our PIs. Warm regards, Yvonne

From: Luc Brion
To: Finer, Neil
Cc: Gantz, Marie; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: Re: Question about Jackie"s study
Date: Saturday, May 04, 2013 6:43:21 AM

Thanks a lot.
I completely eliminated this section in the revised protocol I sent last night.
Best regards
Luc

Sent from my iPhone

On May 4, 2013, at 5:59 AM, "Finer, Neil" <nfiner@ucsd.edu> wrote:

> Hello Luc
> I totally agree with Marie – I would not include the SUPPORT data or infants to this proposal
> She has stated the reasons – and in addition, being in a clinical RCT has been shown to affect outcomes compared with previous baseline populations so I do not think the addition of those babies would be appropriate when looking at changes in practice
> Good luck with this proposal
> Neil
>
> **From:** Gantz, Marie [mailto:mgantz@rti.org]
> **Sent:** Saturday, May 04, 2013 2:30 AM
> **To:** Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann (b)(6) @gmail.com; Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
> **Subject:** RE: Question about Jackie's study
>
> Luc,
>
> My comments on the proposal are attached. As I mentioned in another email, I have reservations about adding data from during SUPPORT to this analysis. I don't think it will help us answer the question of whether there were secular trends, and it could lead us down a path of making comparisons between infants enrolled and not enrolled in SUPPORT which the SUPPORT subcommittee recently voted against. My concerns are described in more detail in comments in the attached document. However, I am happy to discuss further with the group.
>
> Regarding your question below, I don't see an inherent problem with using gestational age and size for gestational age in the models.
>
> Marie
>
> Marie Gantz, Ph.D.
> Senior Research Statistician

RTI International
mgantz@rti.org
919-597-5110

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, April 25, 2013 3:07 PM
To: Gantz, Marie; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Marie;
Thanks a lot and thanks for the discussion.
Hopefully this does not impact the results and is thus not important.
However, if it turns out it is a problem with the data, could we use instead gestational age and size for gestational age (e.g., z score) as was proposed in the protocol?
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, April 25, 2013 2:02 PM
To: Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann; (b)(6) @gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Cc: Gantz, Marie
Subject: RE: Question about Jackie's study

Luc,

I apologize for the delayed response. This week got away from me, but I would be happy to send my thoughts on looking at trends over time next week when I should have more time to think about it.

On the issue of colinearity between GA and BW, although the two are correlated, we

can assess whether that is causing a problem in the model by comparing the estimated effect of covariates in models that include one or both variables. When the sample size is large, it is not necessarily a problem to include both in the model, and by doing so you use more of the available information in the data (as opposed to using SGA). I would also caution that the combination of variables you select can lead to interpretability issues. For example, if BW and SGA (but not GA) are included in a model, then SGA can appear protective because, controlling for BW, the better-off babies are those with higher GA (thus, for a given BW, more likely to be SGA).

I will follow up with you again next week as I am out of the office tomorrow.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-597-5110

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 2:44 PM
To: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie; (b)(6) @gmail.com; 'nfiner@ucsd.edu'; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Wally et al:

Thanks for your email.

I agree with you 100%: we do not consider any pre-specified analyses. All these analyses had been pre-specified in the original protocol.
Lisa, Jackie and I had selected for the poster a set of data from the protocol, which we thought would be the most important for PAS.
The only changes in the protocol I submitted yesterday were those proposed by Lisa, Abhik and Marie during the preparation of the poster, and which have already been incorporated in the results in the poster.

The first analysis in my email today would allow to avoid collinearity between GA and birth weight in all multivariate analyses.
The second analysis addresses secular trends, which is a likely criticism of this manuscript.
The other two analyses are clearly exploratory.

We could definitely stop her and prepare the first draft of the manuscript, or run some of the analyses.

Please let me know what you think.

Best regards,

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 23, 2013 9:37 AM
To: Luc Brion; Wrage, Lisa Ann; Gantz, Marie (b)(6) @gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

We should be careful to add not pre-specified and/or exploratory analyses.

Agree that Marie should be an author.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 9:35 AM
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Gantz, Marie; (b)(6) @gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez

Subject: Question about Jackie's study

Re: Changes over Time in Therapy and Outcomes Associated with The SUPPORT Trial

I sent you yesterday the proposed revision for the protocol for that study.

May I suggest that Marie Gantz, who contributed so much to the poster, should be listed as a co-author.

I would like everyone's opinion whether additional analyses listed in that protocol, but not yet completed, should be conducted before a first draft of a manuscript.

These analyses include:

1. Using SGA or size for age instead of weight in the multivariate models
2. Building a model incorporating years to assess secular trends; this model could include SUPPORT enrollment as covariate
3. Survey of the 11 participating centers (Page 24)
4. Comparing with another network would be a potential next step; I would not include this in a first manuscript.

Should we have a conference call to review this?

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Schulke, Hilda (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: UPDATE | RE: Request for a Conference Call with Drs. Hudson and Koh | Tomorrow, Saturday, May 4 at 3:00 PM
Date: Friday, May 03, 2013 6:22:11 PM
Attachments: image001.png

Thanks - just getting to email-
If needed, I am available

Thanks
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Schulke, Hilda (NIH/OD) [E]
Sent: Friday, May 03, 2013 02:48 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: UPDATE | RE: Request for a Conference Call with Drs. Hudson and Koh | Tomorrow, Saturday, May 4 at 3:00 PM

All:

Per Dr. Hudson John Burklow and Rosemary Higgins don't need to participate in this call so, have a great weekend. I will provide the dial-in info for Dr. Guttmacher and Devaney once we get it.

Thank you,

Hilda

From: Schulke, Hilda (NIH/OD) [E]
Sent: Friday, May 03, 2013 1:21 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Request for a Conference Call with Drs. Hudson and Koh | Tomorrow, Saturday, May 4 at 3:00 PM

Good afternoon all:

Dr. Koh's office is scheduling a conference call on SUPPORT Study for tomorrow Saturday, May 4, 2013 at 3:00 PM. The dial-in information will be provided later. Please confirm your participation.

Thank you,

Hilda

National Institutes of Health
Turning Discovery Into Health

Hilda Schulke | Program Specialist
Office of the Dep Director for Science, Outreach, and Policy
NATIONAL INSTITUTES OF HEALTH
Voice: 301-496-1455| Fax: 301-402-2700
E-mail: Schulkeh@od.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]
Subject: Re: Talking Points.docx
Date: Friday, May 03, 2013 6:17:54 PM

Thanks - hopefully I will represent us well-
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, May 03, 2013 06:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ott, Sandra (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: Talking Points.docx

Rose, here are some talking points for the slides for tomorrow. I am sure you have your own content and will say what you feel is appropriate. I did want to share some of my thoughts with you however. They told me that I could go into the Slide Show as late as tomorrow morning and make any changes we want. I do think the talk is probably too long, so you might want to get rid of some of the slides. Thanks for doing this, I wish could be there. There are several receptions that I would have wanted to attend also, so that I could see some of our PIs. Warm regards, Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -
Date: Friday, May 03, 2013 6:17:21 PM

Is this in the public domain?

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 04:53 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

From: Tyson, Jon E
To: Walsh, Michele; Bell, Edward (Pediatrics); Barbara Stoll; Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; <suhas.kallapur@cchmc.org>, ; <adas@rti.org>, ; <AnnaMaria.hibbs@cwru.edu>, ; " <carl_dangio@urmc.rochester.edu>, " Carlton@ndb-mr2.cc.emory.edu; David P <dpcarlt@emory.edu>, ; <dstevenson@stanford.edu>, ; <edward-bell@uiowa.edu>, ; <gsokol@iupui.edu>, ; John Barks; <vanmeurs@stanford.edu>, ; <kurt.schibler@cchmc.org>, ; <mkeszler@wihri.org>, ; " <mgarg@mednet.ucla.edu>, " Nelin@ndb-mr2.cc.emory.edu; Leif " <Leif.Nelin@nationwidechildrens.org>, " Pablo.Sanchez@UTSouthwestern.edu " <Pablo.Sanchez@utsouthwestern.edu>, " Polin; Richard <rap32@mail.cumc.columbia.edu>, ; " <ronnie_guillet@urmc.rochester.edu>, " Satyan.Lakshminrusimha " <slakshmi@buffalo.edu>, " Schmidt@ndb-mr2.cc.emory.edu; Barbara <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, ; Truog, William (MD); UDEVASKAR@MEDNET.UCLA.EDU; " <wacarlo@uab.edu>, " Archer@ndb-mr2.cc.emory.edu; NIH/NICHD
Subject: RE: REquest for GDB, SUPPORT and FU forms
Date: Friday, May 03, 2013 9:53:47 AM

---

agree

From: Walsh, Michele [Michele.Walsh@UHhospitals.org]
Sent: Friday, May 03, 2013 7:56 AM
To: Bell, Edward (Pediatrics); Barbara Stoll; Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; <suhas.kallapur@cchmc.org>, ; <adas@rti.org>, ; <AnnaMaria.hibbs@cwru.edu>, ; " <carl_dangio@urmc.rochester.edu>, " Carlton@ndb-mr2.cc.emory.edu; David P <dpcarlt@emory.edu>, ; <dstevenson@stanford.edu>, ; <edward-bell@uiowa.edu>, ; <gsokol@iupui.edu>, ; John Barks; Tyson, Jon E; <vanmeurs@stanford.edu>, ; <kurt.schibler@cchmc.org>, ; <mkeszler@wihri.org>, ; " <mgarg@mednet.ucla.edu>, " Nelin@ndb-mr2.cc.emory.edu; Leif " <Leif.Nelin@nationwidechildrens.org>, " Pablo.Sanchez@UTSouthwestern.edu " <Pablo.Sanchez@utsouthwestern.edu>, " Polin; Richard <rap32@mail.cumc.columbia.edu>, ; " <ronnie_guillet@urmc.rochester.edu>, " Satyan.Lakshminrusimha " <slakshmi@buffalo.edu>, " Schmidt@ndb-mr2.cc.emory.edu; Barbara <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, ; Truog, William (MD); UDEVASKAR@MEDNET.UCLA.EDU; " <wacarlo@uab.edu>, " Archer@ndb-mr2.cc.emory.edu; NIH/NICHD
Subject: RE: REquest for GDB, SUPPORT and FU forms

ok

-----Original Message-----
From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Thu 5/2/2013 5:19 PM
To: Barbara Stoll; Kennedy, Kathleen A
Cc: Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; <suhas.kallapur@cchmc.org>, ; <adas@rti.org>, ; <AnnaMaria.hibbs@cwru.edu>, ; " <carl_dangio@urmc.rochester.edu>, " Carlton@ndb-mr2.cc.emory.edu; David P <dpcarlt@emory.edu>, ; <dstevenson@stanford.edu>, ; <edward-bell@uiowa.edu>, ; <gsokol@iupui.edu>, ; John Barks; Tyson, Jon E; <vanmeurs@stanford.edu>, ; <kurt.schibler@cchmc.org>, ; <mkeszler@wihri.org>, ; " <mgarg@mednet.ucla.edu>, " Nelin@ndb-mr2.cc.emory.edu; Leif " <Leif.Nelin@nationwidechildrens.org>, " Pablo.Sanchez@UTSouthwestern.edu " <Pablo.Sanchez@utsouthwestern.edu>, " Polin; Richard <rap32@mail.cumc.columbia.edu>, ; " <ronnie_guillet@urmc.rochester.edu>, " Satyan.Lakshminrusimha " <slakshmi@buffalo.edu>, " Schmidt@ndb-mr2.cc.emory.edu; Barbara <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, ; Truog, William (MD); UDEVASKAR@MEDNET.UCLA.EDU; " <wacarlo@uab.edu>, " Archer@ndb-mr2.cc.emory.edu; NIH/NICHD
Subject: RE: REquest for GDB, SUPPORT and FU forms

All Jack is asking for is to see the data forms, so he can explore submitting a proposal for data analysis. Without knowing the details of what the SUPPORT Subcommittee has already looked at as predictive models, I think the approach Jack would like to use is exciting and novel. Allowing him to see if our database is even amenable to the analyses he has in mind seems a simple enough step with no downside.

Ed

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Sent: Thursday, May 02, 2013 12:39 PM
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Subject: Re: REquest for GDB, SUPPORT and FU forms

Agree with Kathleen and Wally
BJS"Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>> writes:
I don't think that the outcome estimator (survival and survival without NDI) was updated because of the problems with changing the Bayley. Maybe I missed something. I think there are significant questions about the applicability of the BPD calculator based on data from the Benchmarking era. The same might be said about the intubation/surfactant arm of the SUPPORT trial. And there are also questions about generalizability because of the selection bias introduced by antenatal consent. That said, I don't have an objection to allowing Jack and his colleagues to try to use the data. We can pass along our concerns about generalizability.

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Sent: Thursday, May 02, 2013 10:33 AM
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

I feel that we have already done some of this work-

With the updates to the Outcome calculator

And the BPD calculator.

I would be concerned about contradicting our existing work.

How would this expand on what we have done?

Michele

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(wacarlo@uab.edu<mailto:wacarlo@uab.edu>)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: REquest for GDB, SUPPORT and FU forms

Hi-

Jack Sinclair is interested in exploring use of the SUPPORT database to develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD.

See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.

Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

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301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

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Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair
Department of Pediatrics, Emory University School of Medicine
President and CEO, Emory-Children's Center
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hirschfeld, Steven (NIH/NICHD) [E]
Subject: Re: SUPPORT study results in CT.gov?
Date: Friday, May 03, 2013 7:24:32 AM

Let me know if you need anything else
Thanks for your help
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Friday, May 03, 2013 07:15 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT study results in CT.gov?

Got it. Thank you so much, Rose.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD
Captain U.S. Public Health Service

Associate Director for Clinical Research

Director, National Children's Study
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Bethesda, MD

Chief Medical Officer
USPHS Rapid Deployment Force PHS-1

31 Center Drive, Room 2A03
Bethesda, MD 20814

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, May 03, 2013 07:04 AM
To: Hirschfeld, Steven (NIH/NICHD) [E]
Subject: Re: SUPPORT study results in CT.gov?

The issue came up at an HIH workshop several years ago. At the workshop. Dr. Susan McCune

(neonatologist at FDA) stated that the FDA did not regulate oxygen.
Thanks
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Friday, May 03, 2013 06:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT study results in CT.gov?

Rose:

Could you share once more the name of the FDA contact and approximately when you made the inquiry?

Thank you.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD
Captain, U.S. Public Health Service
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
U.S. Public Health Service Rapid Deployment Force PHS-1

31 Center Drive, MSC-2425
Bethesda, MD 20914 (for express packages use 20892)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 02, 2013 2:54 PM
To: Carr, Sarah (NIH/OD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: Re: SUPPORT study results in CT.gov?

Hi Sarah
I just spoke to Steven Hirschfeld. We both agree that SUPPORT is not an applicable FDA clinical trial. Oxygen is not regulated by the FDA and the surfactant was used according to clinical care. Rather, this was a management trial.
As far as the results are concerned, I believe the publications (with links) are in the record. The data coordinating center (RTI) maintains all of the NRN clinicaltrials.gov listings.

Let me know if you need more information.
Thanks for your help

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Carr, Sarah (NIH/OD) [E]
Sent: Thursday, May 02, 2013 02:08 PM
To: Hirschfeld, Steven (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: SUPPORT study results in CT.gov?

Dear Steve and Rose:
We're writing to raise a question to you about the SUPPORT study and whether it owes study results to ClinicalTrials.gov per Title VIII of FDAAA. Since both the oxygen and surfactant that were used in the study are FDA regulated products, it seems to fit the definition of an applicable clinical trial, i.e., a controlled clinical investigation beyond phase 1 of a drug subject to FFDCA. Also, although the record in CT.gov says that the study is still ongoing and that it's estimated to be completed in April 2016, if results are required, we think they should have been submitted one year after all the data for the primary outcome measure was collected. The record indicates that that milestone occurred in February 2009.
In case it's helpful, here's the link to the trial in CT.gov. http://clinicaltrials.gov/ct2/show/NCT00233324?term=NCT00233324&rank=1
And a link to information on Title VIII. http://clinicaltrials.gov/ct2/manage-recs/fdaaa
Another thing that we need to flag is that the record currently lists NICHD, rather than the PI, as the Responsible Party. The Responsible Party is responsible for submitting the results. NIH generally considers grantees to be the sponsors of trials and, therefore, also the Responsible Party. You might want to consult OER's guidance about sponsor and responsible party designations. http://nih-extramural-intranet.od.nih.gov/nih/ClinicalTrials_fdaaa/faqs.html#role1.
You might want to consult Deborah Zarin and Becky Williams at CT.gov to determine for certain whether the SUPPORT study results are required to be submitted.
If you have any questions or wish to discuss, please let us know.
Sarah

Sarah Carr
Office of Clinical Research and Bioethics Policy
NIH Office of Science Policy
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
301-435-6753 (direct)
301-496-9838 (main)
301-496-9839 (fax)
carrs@od.nih.gov

From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Call re:FOIA
Date: Friday, May 03, 2013 5:40:43 AM

Sorry rose- at cdc meeting and was unable to call in -

Pablo
(b)(6) (cell)
(beeper)
214-648-3903 (office)

Sent from iPhone.

On May 1, 2013, at 7:13 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> We will have a call at 1215 ET on thursday May 2.
>
> Call in: (b)(6)
>
>
> Rosemary D. Higgins
> Program Scientist for the NICHD Neonatal Research Network

UT Southwestern Medical Center
The future of medicine, today.

From: Belt, Edward (Pediatrics)
To: Barbara Stoll; Kennedy, Kathleen A
Cc: Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; <suhas.kallapur@cchmc.org>, ; <adas@rti.org>, ; <AnnaMaria.hibbs@cwru.edu>, ; " <carl_dangio@urmc.rochester.edu>, " Carlton@ndb-mr2.cc.emory.edu; David P <dpcarlt@emory.edu>, ; <dstevenson@stanford.edu>, ; <edward-bell@uiowa.edu>, ; <gsokol@iupui.edu>, ; John Barks; Tyson, Jon E; <vanmeurs@stanford.edu>, ; <kurt.schibler@cchmc.org>, ; <mkeszler@wihri.org>, ; " <mgarg@mednet.ucla.edu>, " Nelin@ndb-mr2.cc.emory.edu; Leif " <Leif.Nelin@nationwidechildrens.org>, " Pablo.Sanchez@UTSouthwestern.edu " <Pablo.Sanchez@utsouthwestern.edu>, " Polin; Richard <rap32@mail.cumc.columbia.edu>, ; " <ronnie_guillet@urmc.rochester.edu>, " Satyan.Lakshminrusimha " <slakshmi@buffalo.edu>, " Schmidt@ndb-mr2.cc.emory.edu; Barbara <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, ; Truog, William (MD); UDEVASKAR@MEDNET.UCLA.EDU; " <wacarlo@uab.edu>, " Archer@ndb-mr2.cc.emory.edu; NIH/NICHD
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Date: Thursday, May 02, 2013 5:19:53 PM

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Sent: Thursday, May 02, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa

Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: REquest for GDB, SUPPORT and FU forms

Hi-

Jack Sinclair is interested in exploring use of the SUPPORT database to develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD.

See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.

Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

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Visit us at www.UHhospitals.org.

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair

Department of Pediatrics, Emory University School of Medicine
President and CEO, Emory-Children's Center
SVP and Chief Academic Officer, Children's Healthcare of Atlanta
2015 Uppergate Dr
Atlanta GA 30322
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

Confidential - Please do not forward.

From: Poindexter, Brenda B
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 3:22:31 PM

Rose,
Your request is for yes/no vote to share the forms - for that I would say absolutely yes. Jack's comments, however, imply they want the database and are perhaps asking for NRN collaborators or even help from our statisticians. If this is the request, I say no - if they want data they should bring forward a proposal through usual channels and partner with a participating NRN center to do so.

Just want to be sure we understand what the request is for since you say forms.

Brenda

Sent from my iPhone

On May 2, 2013, at 10:28 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi-
>
> Jack Sinclair is interested in exploring use of the SUPPORT database to develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD.
> See Jack's additional 2 comments about this:
>
> i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.
>
> ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.
> Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Hirschfeld, Steven (NIH/NICHD) [E]
Sent: Thursday, May 02, 2013 2:31 PM
To: Guttmacher, Alan (NIH/NICHD) [E]
Subject: FW: SUPPORT study results in CT.gov?

Another fyi

Steven Hirschfeld, MD PhD
Captain, USPHS
Associate Director for Clinical Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Director
National Children's Study
Chief Medical Officer
USPHS Rapid Deployment Force PHS-1

31 Center Drive
Room 2A03
Bethesda, MD 20814

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, May 02, 2013 2:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: FW: SUPPORT study results in CT.gov?

Hi Steve and Rose – Sarah Carr called me and alerted me that this might be coming. FDA is still looking into whether the SUPPORT trial will need to go ahead and post the trial results as an applicable trial. I guess they will be hearing the final word from FDA. But it is just something to get prepared for and there seems to be some "discussion" as to the applicability in this case.

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Carr, Sarah (NIH/OD) [E]
Sent: Thursday, May 02, 2013 2:08 PM
To: Hirschfeld, Steven (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: SUPPORT study results in CT.gov?

Dear Steve and Rose:

We're writing to raise a question to you about the SUPPORT study and whether (b)(5)
(b)(5)

In case it's helpful, here's the link to the trial in CT.gov.
http://clinicaltrials.gov/ct2/show/NCT00233324?term=NCT00233324&rank=1

And a link to information on Title VIII. http://clinicaltrials.gov/ct2/manage-recs/fdaaa

Another thing that we need to flag is that (b)(5)
(b)(5)

If you have any questions or wish to discuss, please let us know.

Sarah

Sarah Carr
Office of Clinical Research and Bioethics Policy
NIH Office of Science Policy
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892
301-435-6753 (direct)
301-496-9838 (main)
301-496-9839 (fax)
carrs@od.nih.gov

From:	Wally Carlo, M.D.
To:	Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; suhas.kallapur@cchmc.org; alaptook@wihri.org; adas@rti.org; ambal@uab.edu; AnnaMaria.hibbs@cwru.edu; barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; edward-bell@uiowa.edu; goldb008@mc.duke.edu; gsokol@iupui.edu; KIRPALANIH@email.chop.edu; John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; vanmeurs@stanford.edu; kwatterberg@salud.unm.edu; kurt.schibler@cchmc.org; luc.brion@utsouthwestern.edu; mkeszler@wihri.org; mcw3@po.cwru.edu; mgarg@mednet.ucla.edu; Nelin, Leif; Pablo.Sanchez@utsouthwestern.edu; Polin, Richard; rohls@salud.unm.edu; ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; bsood@med.wayne.edu; Truog, William (MD); UDEVASKAR@mednet.ucla.edu; wacarlo@uab.edu
Cc:	Archer, Stephanie (NIH/NICHD) [E]
Subject:	RE: REquest for GDB, SUPPORT and FU forms
Date:	Thursday, May 02, 2013 12:53:21 PM

We also have done a lot of work to predict death in SUPPORT but the SUPPORT subcommittee had decided to stop that work after the initial analysis did not reveal associations between baseline characteristics and death.

From: Walsh, Michele [mailto:Michele.Walsh@uhhospitals.org]
Sent: Thursday, May 02, 2013 10:33 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; suhas.kallapur@cchmc.org; alaptook@wihri.org; adas@rti.org; ambal@uab.edu; AnnaMaria.hibbs@cwru.edu; barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; edward-bell@uiowa.edu; goldb008@mc.duke.edu; gsokol@iupui.edu; KIRPALANIH@email.chop.edu; John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; vanmeurs@stanford.edu; kwatterberg@salud.unm.edu; kurt.schibler@cchmc.org; luc.brion@utsouthwestern.edu; mkeszler@wihri.org; mcw3@po.cwru.edu; mgarg@mednet.ucla.edu; Nelin, Leif; Pablo.Sanchez@utsouthwestern.edu; Polin, Richard; rohls@salud.unm.edu; ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; bsood@med.wayne.edu; Truog, William (MD); UDEVASKAR@mednet.ucla.edu; wacarlo@uab.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

I feel that we have already done some of this work-
With the updates to the Outcome calculator
And the BPD calculator.
I would be concerned about contradicting our existing work.
How would this expand on what we have done?
Michele

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 02, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]

Subject: REquest for GDB, SUPPORT and FU forms

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Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Schulke, Hilda (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Cohen, Paula (NIH/OD) [E]; Mullman, Lauren (NIH/OD) [E]; Jackson, Kendria (NIH/OD) [C]; Hardesty, Rebecca (NIH/OD) [C]
Subject: RE: Today at 4:30 PM | RE: Support study - end game
Date: Thursday, May 02, 2013 12:16:00 PM

HI
I am scheduled to be on a plane at that time – if delayed, I will join

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Schulke, Hilda (NIH/OD) [E]
Sent: Thursday, May 02, 2013 12:15 PM
To: Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Cohen, Paula (NIH/OD) [E]; Mullman, Lauren (NIH/OD) [E]; Jackson, Kendria (NIH/OD) [C]; Hardesty, Rebecca (NIH/OD) [C]
Subject: Today at 4:30 PM | RE: Support study - end game

Good afternoon all:

We are scheduling this meeting for this afternoon from 4:30 PM to 5:00 PM, in Room 103.
Please confirm at your earliest convenience if you are participating in person or by phone.

Thank you,

Hilda

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 01, 2013 10:54 PM
To: Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Schulke, Hilda (NIH/OD) [E]

Subject: Support study - end game

Gang,

I am in a (b)(5) If we in fact reach an agreement on the short statement, NIH needs to (b)(5) (b)(5).

Should we try to get together late tomorrow to talk about outcome goals, strategies, and tactics? We don't have much time since KGS speaks at peds meeting on Monday.

Alan, Rose – I am cc-ing you only to let you know that we are launching this next phase of planning and welcome your ideas and input but don't need to tap anymore of your time/energy in meetings. You guys won the wrestling match and we can pick up the pieces from here. We will check in along the way.

(b)(5)

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 10:42 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Kathy,

This is great to hear! I will look forward to closing up that last micron on our end.

Thanks,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 10:17 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Support study -

Thanks so much Jerry. This marks a real turning point. I have left your edits intact and added our single suggested edit.

I think we may be microns from the finish line.....!

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 6:46 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

Kathy,

Attached are our edits to your version. To stick with your suggestion regarding making things simpler, we first accepted all of your changes, and so the markings only show our changes to what you were most recently proposing.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:11 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much for your response (b)(5)
(b)(5)
(b)(5). However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), I think (b)(5)
(b)(5)

We remain committed to figuring out a path to a good resolution.

Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 11:32:38 AM

Yes.

I think we already did a lot of analysis for death and the committee agreed not to do more exploratory analysis so I would favor that they limit to ROP the analysis. If they propose death analysis, I think the analysis has to be highly hypothesis driven ideally one specific analysis and one specific outcome.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: " (suhas.kallapur@cchmc.org)" <suhas.kallapur@cchmc.org>, "Abbot Laptook (alaptook@wihri.org)" <alaptook@wihri.org>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)" <AnnaMaria.hibbs@cwru.edu>, "barbara_stoll@oz.ped.emory.edu" <barbara_stoll@oz.ped.emory.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "carl_dangio@urmc.rochester.edu" <carl_dangio@urmc.rochester.edu>, "Carlton, David P" <dpcarlt@emory.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "dstevenson@stanford.edu" <dstevenson@stanford.edu>, "dwallace@rti.org" <dwallace@rti.org>, "Ed Bell (edward-bell@uiowa.edu)" <edward-bell@uiowa.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "Greg Sokol (gsokol@iupui.edu)" <gsokol@iupui.edu>, "Haresh Kirpalani (KIRPALANIH@email.chop.edu)" <KIRPALANIH@email.chop.edu>, John Barks <jbarks@med.umich.edu>, "Jon.E.Tyson@uth.tmc.edu" <Jon.E.Tyson@uth.tmc.edu>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Krisa Van Meurs (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, "Kristi Watterberg (kwatterberg@salud.unm.edu)" <kwatterberg@salud.unm.edu>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, "Luc Brion (luc.brion@utsouthwestern.edu)" <luc.brion@utsouthwestern.edu>, "Martin Keszler (mkeszler@wihri.org)" <mkeszler@wihri.org>, "mcw3@po.cwru.edu" <mcw3@po.cwru.edu>, "Meena Garg (mgarg@mednet.ucla.edu)" <mgarg@mednet.ucla.edu>, "Nelin, Leif" <Leif.Nelin@nationwidechildrens.org>, "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@utsouthwestern.edu>, "Polin, Richard" <rap32@mail.cumc.columbia.edu>, "Robin Ohls (rohls@salud.unm.edu)" <rohls@salud.unm.edu>, "ronnie_guillet@urmc.rochester.edu" <ronnie_guillet@urmc.rochester.edu>, Satyan Lakshminrusimha <slakshmi@buffalo.edu>, "Schmidt, Barbara (Neonatology)" <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, "Sood, Beena [bsood@med.wayne.edu]" <bsood@med.wayne.edu>, "Truog, William (MD)" <wtruog@cmh.edu>, "Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU)" <UDEVASKAR@mednet.ucla.edu>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>
Cc: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>
Sent: Thu, May 2, 2013 14:28:40 GMT+00:00

Subject: REquest for GDB, SUPPORT and FU forms

Hi-

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Please send me a yes/no vote by May 10 to share the forms with Jack and Maura Marcucci at McMaster.

Thanks
Rose

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 11:06:00 AM

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Kristi Watterberg [mailto:kwatterberg@salud.unm.edu]
Sent: Thursday, May 02, 2013 11:02 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: REquest for GDB, SUPPORT and FU forms

Yes, and I'm interested in participating. Kristi

Sent from my iPhone

On May 2, 2013, at 8:28 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi-
>
> Jack Sinclair is interested in exploring use of the SUPPORT database to develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD.
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 11:01:00 AM

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-435-7909
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Thursday, May 02, 2013 11:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: REquest for GDB, SUPPORT and FU forms

Yes

On May 2, 2013, at 9:29 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi-
>
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 10:46:00 AM

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: D'Angio, Carl [mailto:Carl_Dangio@URMC.Rochester.edu]
Sent: Thursday, May 02, 2013 10:44 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

Yes.

Carl

Carl T. D'Angio, MD
Professor of Pediatrics and Medical Humanities & Bioethics
Director, Neonatal Clinical Research
Director, Pediatric Clinical Research Office
Director, Ethics Key Function, URMC CTSI
Division of Neonatology, Golisano Children's Hospital
University of Rochester Medical Center
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 02, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; D'Angio, Carl; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); Guillet, Ronnie; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)

Cc: Archer, Stephanie (NIH/NICHD) [E]
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 10:39:00 AM

I am a yes--

Rosemary D. Higgins, MD
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From: Laptook, Abbot [mailto:ALaptook@Wihri.org]
Sent: Thursday, May 02, 2013 10:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

Yes. AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 02, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Laptook, Abbot; Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Keszler, Martin; mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: REquest for GDB, SUPPORT and FU forms
Date: Thursday, May 02, 2013 10:30:00 AM

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, May 02, 2013 10:30 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: REquest for GDB, SUPPORT and FU forms

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 02, 2013 10:28 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Das, Abhik; Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); [SCRN] Stoll, Barbara; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; Wallace, Dennis; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Re: Support study - end game
Date: Thursday, May 02, 2013 7:39:39 AM

Secretary of hhs
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

----- Original Message -----
From: Willinger, Marian (NIH/NICHD) [E]
Sent: Thursday, May 02, 2013 07:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support study - end game

Terrific- well done!
Who is KGS?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 02, 2013 6:16 AM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: Support study - end game

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 01, 2013 10:53 PM
To: Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Schulke, Hilda (NIH/OD) [E]
Subject: Support study - end game

Gang,

I am (b)(5) If we in fact reach an agreement on the short statement, NIH needs t(b)(5)
(b)(5)

Should we try to get together late tomorrow to talk about outcome goals, strategies, and tactics? We don't have much time since KGS speaks at peds meeting on Monday.

Alan, Rose – I am cc-ing you only to let you know that we are launching this next phase of planning and welcome your ideas and input but don't need to tap anymore of your time/energy in meetings. You guys won the wrestling match and we can pick up the pieces from here. We will check in along the way.

(b)(5)

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 10:42 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)

Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Kathy,

This is great to hear! I will look forward to closing up that last micron on our end.

Thanks,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 10:17 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Support study -

Thanks so much Jerry. This marks a real turning point. I have left your edits intact and added our single suggested edit.

I think we may be microns from the finish line.....!

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 6:46 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

Kathy,

Attached are our edits to your version. To stick with your suggestion regarding making things simpler, we first accepted all of your changes, and so the markings only show our changes to what you were most recently proposing.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:11 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much for your response to (b)(5)

(b)(5)

(b)(5) However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), I think (b)(5)

(b)(5)

We remain committed to figuring out a path to a good resolution.

Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: NIH support summary - nih response
Date: Wednesday, May 01, 2013 6:56:10 PM

Can they delete:

(b)(5)

This may be an option- what do others think?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 06:46 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

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From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:11 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much for your response to (b)(5)

(b)(5)

(b)(5) However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), I think (b)(5)

(b)(5)

the consent form for parents.

We remain committed to figuring out a path to a good resolution.

Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

From: Bell, Edward (Pediatrics)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Call re:FOIA
Date: Wednesday, May 01, 2013 7:12:58 PM

Thanks

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 01, 2013 6:12 PM
To: 'AnnaMaria.hibbs@cwru.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'KIRPALANIH@email.chop.edu'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Leif.Nelin@nationwidechildrens.org'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'UDEVASKAR@MEDNET.UCLA.EDU'; 'adas@rti.org'; 'alaptook@wihri.org'; 'ambal@uab.edu'; 'barbara.schmidt@uphs.upenn.edu'; 'barbara_stoll@oz.ped.emory.edu'; 'bpoindex@iupui.edu'; 'bsood@med.wayne.edu'; 'carl_dangio@urmc.rochester.edu'; 'cotte010@mc.duke.edu'; 'dpcarlt@emory.edu'; 'dstevenson@stanford.edu'; 'dwallace@rti.org'; Bell, Edward (Pediatrics); 'goldb008@mc.duke.edu'; 'gsokol@iupui.edu'; 'jbarks@med.umich.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'luc.brion@utsouthwestern.edu'; 'mcw3@po.cwru.edu'; 'mgarg@mednet.ucla.edu'; 'mkeszler@wihri.org'; 'rap32@mail.cumc.columbia.edu'; 'rohls@salud.unm.edu'; 'ronnie_guillet@urmc.rochester.edu'; 'slakshmi@buffalo.edu'; 'sshankar@med.wayne.edu'; 'suhas.kallapur@cchmc.org'; 'vanmeurs@stanford.edu'; 'wacarlo@uab.edu'; 'wtruog@cmh.edu'; Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; 'mcunningham@rti.org'
Subject: Call re:FOIA

We will have a call at 1215 ET on thursday May 2.

Call in: (b)(6)

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NIH support summary - nih response
Date: Wednesday, May 01, 2013 7:28:06 AM

I am sorry that I didn't check my email last night to weigh in on this. Hopefully (b)(5) if you have a chance to give more input I would consider leaving out the sentence about the sample consent.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, May 01, 2013 5:55 AM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: NIH support summary - nih response

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 01, 2013 12:19 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

Fyi

Fc and I discussed this late tonight before I sent response to jerry so what was sent had his full blessing. I cc'd fc so howard et al would know fc was on board. fc will send note to bill corr tonight updating him that (b)(5)
(b)(5)

Really grateful for all the time and intelligence you all are investing in this.

Nite,
kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, May 01, 2013 12:11 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much for your response (b)(5)
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(b)(5) However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), I think (b)(5)
(b)(5)

We remain committed to figuring out a path to a good resolution.

Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work

through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: NIH support summary - nih response
Date: Wednesday, May 01, 2013 6:37:08 AM

FYI
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 06:20 AM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: NIH support summary - nih response

Kathy,

Thank you for all of your work on this. On our end, we share your commitment to produce a mutually acceptable resolution to this, and will be getting back to you with that in mind.

Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:10 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

Hi Jerry,

Thanks so much for your response (b)(5)
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(b)(5) However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), I think (b)(5)
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Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

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Jerry

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: NIH support summary - nih response
Date: Wednesday, May 01, 2013 6:37:07 AM

FYI

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Koh, Howard (HHS/OASH)
Sent: Wednesday, May 01, 2013 06:18 AM
To: Hudson, Kathy (NIH/OD) [E]; Menikoff, Jerry (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

Thank you Kathy and colleagues.

I am seeing Bill at 9:30 this morning for my regular meeting.
I have already shared by email to him that we made substantial progress yesterday- let's see what he advises.

I am willing to host more calls today to get this process over the finish line, if at all possible.
Thank you Kathy and colleagues for working so hard on this. We appreciated the good dialogue yesterday and still hope this can be resolved. Howard

---

From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:10 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: NIH support summary - nih response

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(b)(5) However, at the end of the day (and my clock reads 11:59 pm so it truly is the end of the day), I think (b)(5)
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Thanks Howard and team for a productive series of discussions today. We really appreciated being able to work through the issues with you.

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, April 30, 2013 8:48 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Willinger, Marian (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: RE: NIH support summary
Attachments: Follow-up SUPPORT letter 2NICHD edits.docx

Here is the consolidated NICHD version, with all of Jerry's edits accepted and ours then shown in track change mode. Edits look more massive than they might because sections were moved in an effort to improve the logic of the letter's flow.

Alan

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 6:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

Page 1696 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1697 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Spong, Catherine (NIH/NICHD) [E]
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NIH support summary
Date: Tuesday, April 30, 2013 7:57:17 PM

Sorry I just saw this
Just to confirm, this a letter from OHRP to the UAB IRB, yes?

Paragraph 3: I don't (b)(5)
(b)(5)

Paragraph 4, I don' (b)(5)
(b)(5)

Paragraph 5: I would suggest removing (b)(5)
(b)(5)

Paragraph 5: will the information in the "( )" be included?

Paragraph 6, I am not certain what this paragraph adds – not certain (b)(5)
(b)(5)

Cathy

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, April 30, 2013 6:17 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: NIH support summary

Thoughts (ASAP)?

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health

31 Center Drive, Room 2A03
Bethesda, MD 20892-2425
Phone:301-496-3454
e-mail: guttmach@mail.nih.gov
url: nichd.nih.gov

From: Menikoff, Jerry (HHS/OASH)
Sent: Tuesday, April 30, 2013 06:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH support summary

Kathy,

Attached, as we discussed, is a mark-up of your document.

Best,
Jerry

From: Rich, Wade
To: Wally Carlo, M.D.; Jack Sinclair; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT analysis idea
Date: Tuesday, April 30, 2013 5:56:30 PM

Neil said to let you know he is supportive, and apologizes for email issues.
wade

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 12:11 PM
To: Jack Sinclair; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org; Rich, Wade
Cc: Rosemary Higgins
Subject: RE: SUPPORT analysis idea

Wade:

Can you forward this email to Neil? He is not getting them.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Jack Sinclair [mailto:sinclair@mcmaster.ca]
Sent: Tuesday, April 30, 2013 2:04 PM
To: Wally Carlo, M.D.; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: Re: SUPPORT analysis idea

Wally:
I'm so happy you find the proposal interesting and potentially important!

Curiously, Ed's email to Neil Finer was returned on my computer as undeliverable. I'm not sure whether he received it. In any event, I haven't heard from Neil and I believe we do need his support if this is to proceed.

Jack

> ----- Original Message -----
> **From:** Wally Carlo, M.D.
> **To:** Jack Sinclair ; Bell, Edward (Pediatrics) ; Finer, Neil ; mgantz@rti.org
> **Cc:** Rosemary Higgins

Sent: Tuesday, April 30, 2013 2:17 PM
Subject: RE: SUPPORT analysis idea

Jack:

That is the correct abstract. I looked at the paper you mentioned. I see the difference in the analysis.

I think your proposal is an interesting one that may yield very important information.

Wally

From: Jack Sinclair [mailto:sinclair@mcmaster.ca]
Sent: Tuesday, April 30, 2013 1:03 PM
To: Bell, Edward (Pediatrics); Wally Carlo, M.D.; Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: Re: SUPPORT analysis idea

Thanks, Ed.

Wally: re the PAS abstract from about 2 years ago that you refer to - is that the one titled ROP and actual oxygen saturations in the SUPPORT trial [2011] [1660.4]? That concerned the development of a predictive model for severe ROP based largely on data not yet available at the time the randomized treatment was instituted (percent of days on O2 therapy, percent of time in various SpO2 ranges). And it did not include the prediction of individualized treatment effects. I look forward to seeing your manuscript when you can share it. But I don't understand in what way it overlaps our proposal. Am I looking at the wrong PAS abstract?

It would indeed be much more powerful to develop models for individualizing predictions of baseline risks and oxygen treatment effects for severe ROP, BPD and death using the data from all 5 trials in the prospective meta-analysis group. That's getting into the league of internal medicine (Dorresteijn et al, BMJ 2011) who developed such individualized predictions on over 17,000 patients provided by a single trial (JUPITER, rosuvastatin for prevention of CV events)!

Jack

----- Original Message -----
From: Bell, Edward (Pediatrics)
To: Wally Carlo, M.D. ; Finer, Neil ; 'mgantz@rti.org'
Cc: Sinclair, Jack ; Rosemary Higgins
Sent: Tuesday, April 30, 2013 11:05 AM
Subject: RE: SUPPORT analysis idea

OK, thanks. Once you can share your manuscript with Jack, he can consider if his proposed approach might add new insights. It seems that it might. If so, we might propose again sharing the data forms with Jack and Maura.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 10:01 AM
To: Bell, Edward (Pediatrics); Finer, Neil; 'mgantz@rti.org'
Cc: Sinclair, Jack; Rosemary Higgins
Subject: RE: SUPPORT analysis idea

Ed:

We have two such protocols although the methods may differ.

The analyses for the ROP protocol has been completed and is as manuscript draft now. I drafted the intro and methods. Marie is doing the results and discussion and will be first author as the analyses were more complex than initially planned. I am copying her.

The analysis for mortality did not yield results associations even with some exploratory analyses. The committee decided that the associations would be weak and that the analysis should not continue.

I think an opportunity would be to work with the prospective meta-analysis group. At some point soon, they will have all the data from the 5 trials. 5 of us from the NRN are active members of that group so we can help facilitate it.

Jack:

I think this is a very important area. I presented an abstract at PAS about two years ago on this and that is the paper we are working on.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, April 30, 2013 9:51 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Sinclair, Jack; Rosemary Higgins
Subject: SUPPORT analysis idea

Dear Wally and Neil,
Jack Sinclair is interested in exploring use of the SUPPORT database develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe

ROP, and BPD. I think this might be an important first step toward learning how to set oxygen saturation targets that are personalized for individual patients. Jack gave me permission to share the attached unpublished manuscript with you – in confidence, of course.

See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.

If you agree this idea is worth exploring, I will ask Rose to seek SC approval to share the SUPPORT data forms with Jack and his colleague and coauthor Maura Marcucci at McMaster, so they can see exactly which data elements are available in the SUPPORT database.

Thanks,
Ed

Notice: This UI Health Care e-mail (including attachments) is covered by the Electronic Communications Privacy Act, 18 U.S.C. 2510-2521, is confidential and may be legally privileged. If you are not the intended recipient, you are hereby notified that any retention, dissemination, distribution, or copying of this communication is strictly prohibited. Please reply to the sender that you have received the message in error, then delete it. Thank you.

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, April 30, 2013 5:21 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Latest SUPPORT call with Howard and Jerry

Hi Francis –

Alan, Rose, Steph, and I talked with Howard, Jerry, and a few others from OHRP at 3:15. They had our 8 bullets and Jerry had been asked to come to the call ready to react to them.

It was a very productive call actually – I think (b)(5) (b)(5) We walked through the points on the call. Below are our 8 bullets with our notations in red showing what OHRP said during the call. The next step is for Jerry to mark up these points and send them back around. Howard has a meeting with Bill tomorrow morning and wants to at least be able to say that we're *this* close. The need to move quickly is still there – the Pediatric Academic Societies are having their annual meeting in DC beginning on Saturday and the Secretary is scheduled to speak on Monday.

1. (b)(5)
2.
3.
4.
5.
6.

7. (b)(5)

8.

Will keep you posted.

From: Stevens, Timothy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: PEDIATRICS: Decision Letter - MS# 2013-0756
Date: Tuesday, April 30, 2013 1:04:46 PM
Attachments: Decision-Letter-Attachment-10-16-12.doc

Hi Rose

Here is the decision from Pediatrics about the Breathing Outcomes manuscript. Most of the comments are easily addressed. The two toughest are from the editor, does each coauthor meet authorship criteria and please address the "ethical concerns" of SUPPORT.

I'll draft a revised manuscript that responds to the reviewers concerns.

I'd appreciate your thoughts.

Thanks

Tim

----Original Message-----
From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com [mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of PediatricsEditorial@aap.org
Sent: Tuesday, April 30, 2013 9:59 AM
To: Stevens, Timothy
Subject: PEDIATRICS: Decision Letter - MS# 2013-0756

30-Apr-2013

RE: MS# 2013-0756

Title: Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial

Authors: Stevens, Timothy; Finer, Neil; Carlo, Waldemar; Szilagyi, Peter; Phelps, Dale; Walsh, Michele; Gantz, Marie; Laptook, Abbot; Yoder, Bradley; Faix, Roger; Newman, Jamie; Das, Abhik; Do, Barbara; Schibler, Kurt; Rich, Wade; Newman, Nancy; Ehrenkranz, Richard; Peralta-Carcelen, Myriam; Vohr, Betty R.; Wilson-Costello, Deanne; Yolton, Kimberly; Heyne, Roy; Dusick, Anna; Evans, Patricia; Vaucher, Yvonne; Adams-Chapman, Ira; McGowan, Elisabeth; Bodnar, Anna; Pappas, Athina; Hintz, Susan; Acarregui, Michael; Fuller, Janell; Goldstein, Rikki; Bauer, Charles; O'Shea, Thomas; Myers, Gary; Higgins, Rosemary

Dear Dr. Stevens:

The editors of Pediatrics feel that your manuscript may have merit but would require substantial work before it could be seriously considered for publication. You are welcome to submit a revised manuscript, which will be sent out for peer review; referees may include past and new reviewers. Please be aware that fewer than half of such papers are ultimately accepted.

If you decide to resubmit this manuscript, you must address the concerns of the reviewers at the end of this e-mail. Your successful response to the critiques of the current reviewers does not guarantee acceptance of the manuscript, because new reviewers may be added for the revised paper and may have different concerns.

In addition to the reviewers' comments below, please address the following items from the editors:

1) It appears that not (b)(4)

2) Please address the

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewers and the editors in the space provided under "Author's Response." You can use this space to document any additional changes you make to the original manuscript. In addressing any substantive suggestions or criticisms made by our reviewers, please make a numerical listing of what you have done, or not done, in regard to each suggestion of the reviewers. If the reviewer's request is for clarification, please make the clarification in the text of the paper. Remember that explaining what you mean to the editors and reviewers does not help the reader.

Your revision should be submitted via http://mc.manuscriptcentral.com/pediatrics. In your "Author Center," click on "Manuscripts with Decisions." In the "Actions" box, click on "Create a Revision." Please upload the revised version of your manuscript and delete the older version from the system before completing the submission. The revised manuscript should have no editing tags; it should be an unmarked version without margin notes or boldface notes. Once submitted, your revised manuscript's number will be appended to denote a particular revision (R1, R2, etc).

If you choose to do so, a revised manuscript must be submitted within 90 (ninety) days of this date. You can monitor the time remaining through your Author Center.

For additional requirements, see the attached document.

Sincerely,

Lewis R. First, MD
Editor-in-Chief, Pediatrics
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics, Vermont Children's Hospital at Fletcher Allen Health Care
802-656-0027 (office)
802-656-2077 (fax)
lewis.first@uvm.edu

Reviewer: 1

The authors aimed to assess the long term respiratory outcomes from VLBW patients treated in the previously reported NICHD SUPPORT Trial. This is an important and valid research question, an appropriately large cohort, followed with rigorous methodology and the results are important:

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer: 2

Thank you for the opportunity to review Stevens' and colleagues manuscript, "Respiratory outcomes of the early CPAP and pulse oximetry trial".

The NICHD SUPPORT Trial using a (b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer: 3

This is a (b)(4),(b)(6)

(b)(4),(b)(6)

Page 1711 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

ADDITIONAL REQUIREMENTS FOR AUTHORS

CLINICAL TRIALS--If you are reporting the results of a clinical trial, you must affirm that the study has been registered at www.clinicaltrials.gov or another qualified national or international registry, and include the study registration number on your title page.

Timing of clinical trial registration: Clinical trials must have been registered **before** the first patient was enrolled. If you did not do so, contact the editors.

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FINANCIAL DISCLOSURES--Also required on the title page, this information deals specifically with author declarations.

CONFLICTS OF INTEREST--This information must be included in the custom questions on our website and also on the title page of your paper.

ABSTRACT--If your abstract is changed during revision, the changes must be made not only in the manuscript document, but also in the Scholar One abstract box. These abstract versions must be identical.

Abstract length: A 250-word maximum applies to all types of manuscripts. 250 words = 1570 characters including spaces. Abstracts are not required for commentaries.

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"WHAT'S KNOWN ON THIS SUBJECT" and "WHAT THIS STUDY ADDS"
Required for Regular Articles only, these two summaries will become highly visible, with prominence on the first page of the published article. These summaries will also be highlighted and presented in other areas of the journal, particularly Pediatrics Digest. It is therefore paramount that you enter precise, accurate language in these two Scholar One

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From: Willinger, Marian (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: futile task to revise ohrp letter to uab
Date: Tuesday, April 30, 2013 7:44:20 AM

Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, April 30, 2013 6:18 AM
To: Willinger, Marian (NIH/NICHD) [E]
Subject: Fw: futile task to revise ohrp letter to uab

Fyi
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, April 29, 2013 10:07 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: futile task to revise ohrp letter to uab

I can see this exercise was pretty frustrating.

So let's regroup. I didn't (b)(5)
(b)(5)

So instead, let's try for a (b)(5)
Something like:

(b)(5)

How does that sound?

FC

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, April 29, 2013 9:55 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: futile task to revise ohrp letter to uab

Francis,
I tried to correct the (b)(5) I spent quite a while on this. I quit on page 11. I am going (b)(5)

A revised letter won't work.

The only other approach is for ohrp to say:

(b)(5)

Ugh.

I need to become an advocate....

From: Bell, Edward (Pediatrics)
To: Rich, Wade; Wally Carlo, M.D.; Jack Sinclair; Finer, Neil; mgantz@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT analysis idea
Date: Tuesday, April 30, 2013 6:00:02 PM

Thanks, Wade. Rose, I think the next step is to seek SC approval of sharing the SUPPORT and GDB data forms with Jack and Maura. I think they might need to look at the FU forms, too.

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Tuesday, April 30, 2013 4:56 PM
To: Wally Carlo, M.D.; Jack Sinclair; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: RE: SUPPORT analysis idea

Neil said to let you know he is supportive, and apologizes for email issues.
wade

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 12:11 PM
To: Jack Sinclair; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org; Rich, Wade
Cc: Rosemary Higgins
Subject: RE: SUPPORT analysis idea

Wade:

Can you forward this email to Neil? He is not getting them.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell (b)(6)

From: Jack Sinclair [mailto:sinclair@mcmaster.ca]
Sent: Tuesday, April 30, 2013 2:04 PM
To: Wally Carlo, M.D.; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: Re: SUPPORT analysis idea

Wally:
I'm so happy you find the proposal interesting and potentially important!

Curiously, Ed's email to Neil Finer was returned on my computer as undeliverable. I'm not sure whether he received it. In any event, I haven't heard from Neil and I believe we do need his support if this is to proceed.

Jack

----- Original Message -----
From: Wally Carlo, M.D.
To: Jack Sinclair ; Bell, Edward (Pediatrics) ; Finer, Neil ; mgantz@rti.org
Cc: Rosemary Higgins
Sent: Tuesday, April 30, 2013 2:17 PM
Subject: RE: SUPPORT analysis idea

Jack:

That is the correct abstract. I looked at the paper you mentioned. I see the difference in the analysis.

I think your proposal is an interesting one that may yield very important information.

Wally

From: Jack Sinclair [mailto:sinclair@mcmaster.ca]
Sent: Tuesday, April 30, 2013 1:03 PM
To: Bell, Edward (Pediatrics); Wally Carlo, M.D.; Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: Re: SUPPORT analysis idea

Thanks, Ed.

Wally: re the PAS abstract from about 2 years ago that you refer to - is that the one titled ROP and actual oxygen saturations in the SUPPORT trial [2011] [1660.4]? That concerned the development of a predictive model for severe ROP based largely on data not yet available at the time the randomized treatment was instituted (percent of days on O2 therapy, percent of time in various SpO2 ranges). And it did not include the prediction of individualized treatment effects. I look forward to seeing your manuscript when you can share it. But I don't understand in what way it overlaps our proposal. Am I looking at the wrong PAS abstract?

It would indeed be much more powerful to develop models for individualizing predictions of baseline risks and oxygen treatment effects for severe ROP, BPD and death using the data from all 5 trials in the prospective meta-analysis group. That's getting into the league of internal medicine (Dorresteijn et al, BMJ 2011) who developed such individualized predictions on over 17,000 patients provided by a single trial (JUPITER, rosuvastatin for prevention of CV events)!

Jack

----- Original Message -----
From: Bell, Edward (Pediatrics)
To: Wally Carlo, M.D. ; Finer, Neil ; 'mgantz@rti.org'
Cc: Sinclair, Jack ; Rosemary Higgins
Sent: Tuesday, April 30, 2013 11:05 AM
Subject: RE: SUPPORT analysis idea

OK, thanks. Once you can share your manuscript with Jack, he can consider if his proposed approach might add new insights. It seems that it might. If so, we might propose again sharing the data forms with Jack and Maura.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 10:01 AM
To: Bell, Edward (Pediatrics); Finer, Neil; 'mgantz@rti.org'
Cc: Sindair, Jack; Rosemary Higgins
Subject: RE: SUPPORT analysis idea

Ed:

We have two such protocols although the methods may differ.

The analyses for the ROP protocol has been completed and is as manuscript draft now. I drafted the intro and methods. Marie is doing the results and discussion and will be first author as the analyses were more complex than initially planned. I am copying her.

The analysis for mortality did not yield results associations even with some exploratory analyses. The committee decided that the associations would be weak and that the analysis should not continue.

I think an opportunity would be to work with the prospective meta-analysis group. At some point soon, they will have all the data from the 5 trials. 5 of us from the NRN are active members of that group so we can help facilitate it.

Jack:

I think this is a very important area. I presented an abstract at PAS about two years ago on this and that is the paper we are working on.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, April 30, 2013 9:51 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Sinclair, Jack; Rosemary Higgins
Subject: SUPPORT analysis idea

Dear Wally and Neil,
Jack Sinclair is interested in exploring use of the SUPPORT database develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD. I think this might be an important first step toward learning how to set oxygen saturation targets that are personalized for individual patients. Jack gave me permission to share the attached unpublished manuscript with you – in confidence, of course.

See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.

If you agree this idea is worth exploring, I will ask Rose to seek SC approval to share the SUPPORT data forms with Jack and his colleague and coauthor Maura Marcucci at McMaster, so they can see exactly which data elements are available in the SUPPORT database.

Thanks,
Ed

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; "edward-bell@uiowa.edu"; "sinclair@mcmaster.ca"; "nfiner@ucsd.edu"; "mgantz@rti.org"
Subject: RE: SUPPORT analysis idea
Date: Tuesday, April 30, 2013 4:07:43 PM

Yeah> That would be helpful.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 30, 2013 2:57 PM
To: Wally Carlo, M.D.; 'edward-bell@uiowa.edu'; 'sinclair@mcmaster.ca'; 'nfiner@ucsd.edu'; 'mgantz@rti.org'
Subject: Re: SUPPORT analysis idea

Yew- would you like me to request?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 03:15 PM
To: Bell, Edward (Pediatrics) <edward-bell@uiowa.edu>; Jack Sinclair <sinclair@mcmaster.ca>; Finer, Neil <nfiner@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT analysis idea

Rose:

Do we need permission from the SC to share the SUPPORT data collection forms? I guess he will also need the GDB forms.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R

Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, April 30, 2013 2:12 PM
To: Jack Sinclair; Wally Carlo, M.D.; Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: RE: SUPPORT analysis idea

I agree we should wait to hear from Neil, but if he agrees, we can ask Rose to seek Steering Committee approval to share the SUPPORT data forms with Jack and Maura. Several of us have had our e-mails to Neil bounce back, but Rose has sent at least one of these messages to him through Wade Rich, a colleague of Neil's at UCSD.
Ed

From: Jack Sinclair [mailto:sinclair@mcmaster.ca]
Sent: Tuesday, April 30, 2013 2:04 PM
To: Wally Carlo, M.D.; Bell, Edward (Pediatrics); Finer, Neil; mgantz@rti.org
Cc: Rosemary Higgins
Subject: Re: SUPPORT analysis idea

Wally:
I'm so happy you find the proposal interesting and potentially important!

Curiously, Ed's email to Neil Finer was returned on my computer as undeliverable. I'm not sure whether he received it. In any event, I haven't heard from Neil and I believe we do need his support if this is to proceed.

Jack

> ----- Original Message -----
> **From:** Wally Carlo, M.D.
> **To:** Jack Sinclair ; Bell, Edward (Pediatrics) ; Finer, Neil ; mgantz@rti.org
> **Cc:** Rosemary Higgins
> **Sent:** Tuesday, April 30, 2013 2:17 PM
> **Subject:** RE: SUPPORT analysis idea
>
> Jack:
>
> That is the correct abstract. I looked at the paper you mentioned. I see the difference in the analysis.
>
> I think your proposal is an interesting one that may yield very important information.
>
> Wally
>
> ---
>
> **From:** Jack Sinclair [mailto:sinclair@mcmaster.ca]
> **Sent:** Tuesday, April 30, 2013 1:03 PM
> **To:** Bell, Edward (Pediatrics); Wally Carlo, M.D.; Finer, Neil; mgantz@rti.org
> **Cc:** Rosemary Higgins

Subject: Re: SUPPORT analysis idea

Thanks, Ed.

Wally: re the PAS abstract from about 2 years ago that you refer to - is that the one titled ROP and actual oxygen saturations in the SUPPORT trial [2011] [1660.4]? That concerned the development of a predictive model for severe ROP based largely on data not yet available at the time the randomized treatment was instituted (percent of days on O2 therapy, percent of time in various SpO2 ranges). And it did not include the prediction of individualized treatment effects. I look forward to seeing your manuscript when you can share it. But I don't understand in what way it overlaps our proposal. Am I looking at the wrong PAS abstract?

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Jack

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From: Bell, Edward (Pediatrics)
To: Wally Carlo, M.D. ; Finer, Neil ; 'mgantz@rti.org'
Cc: Sinclair, Jack ; Rosemary Higgins
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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 10:01 AM
To: Bell, Edward (Pediatrics); Finer, Neil; 'mgantz@rti.org'
Cc: Sinclair, Jack; Rosemary Higgins
Subject: RE: SUPPORT analysis idea

Ed:

We have two such protocols although the methods may differ.

The analyses for the ROP protocol has been completed and is as manuscript draft now. I drafted the intro and methods. Marie is doing the results and discussion and will be first author as the analyses were more complex than initially planned. I am copying her.

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(b)(5)

Jack:

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Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, April 30, 2013 9:51 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Sinclair, Jack; Rosemary Higgins
Subject: SUPPORT analysis idea

Dear Wally and Neil,
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Thanks,
Ed

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From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP ver 6 0 (03-28-2013)_changesaccepted
Date: Tuesday, April 30, 2013 1:46:53 PM

Yes.

THX!

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 30, 2013 12:45 PM
To: nfiner@ucsd.edu; Wally Carlo, M.D.; Wade RIch; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh (mcw3@cwru.edu); Roger Faix (Roger.Faix@hsc.utah.edu); Abbot Laptook; Brad Yoder (Bradley.yoder@hsc.utah.edu); Myriam Peralta, M.D.; Yvonne Vaucher; Abhik Das (adas@rti.org); mgantz@rti.org; nxs5@case.edu
Subject: ROP ver 6 0 (03-28-2013)_changesaccepted

Hi
Wally has asked to share this confidential draft of a SUPPORT secondary with Jack Sinclair. Jack is interested in determining predictors of ROP. Please send me a yes/no vote to share by May 6.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Lewis-Evans, Amanda"
Subject: RE: Review Requested: Notes from SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET
Date: Tuesday, April 30, 2013 1:43:00 PM

Perfect!!

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Lewis-Evans, Amanda [mailto:alewis@rti.org]
Sent: Tuesday, April 30, 2013 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Lewis-Evans, Amanda
Subject: Review Requested: Notes from SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET

Hi Rose,

Please review and revise the attached notes as needed.

Thank you,

Amanda

From: Gabrio, Jenna
Sent: Thursday, April 25, 2013 11:35 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; Yvonne Vaucher; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; Becky Brazeel; 'Brenda Vecchio'; Cunningham, Meg; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET

Dear all,

Thank you all for your quick responses. Please find the call details below and remember that the participant passcode has recently been updated.

The SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group

relative to that in non-enrolled eligible babies has been schedule for:

Monday, 4/29
3:00pm ET

Dial:
Within the USA
(b)(6)

or

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abbot, Michele and Yvonne will be unable to join.

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Wednesday, April 24, 2013 9:14 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.

Please provide your availability for the following dates on the Doodle poll (http://www.doodle.com/48dpg9qq6f8peq8f):

4/25, Th
4/26, F

4/29, M
4/30, Tu
5/1, W
5/2, Th

5/3, F

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Brown, Crystal (NIH/NICHD) [C]
Subject: RE: SUPPORT call at 3:15
Date: Tuesday, April 30, 2013 1:21:00 PM

I will come over – spoke to Kathy earlier

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Tuesday, April 30, 2013 1:17 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hudson, Kathy (NIH/OD) [E]; Brown, Crystal (NIH/NICHD) [C]
Subject: SUPPORT call at 3:15

Hi Rose and Alan –

Howard Koh's office sent the call in info for the 3:15 call. I'm not sure if you're joining us in Kathy's office or calling in.

When: Tuesday, April 30, 2013 3:15 PM-3:45 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Dial-in-Number (b)(6) **Passcode** (b)(6)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, April 30, 2013 12:32 PM
To: Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Menikoff, Jerry (HHS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: NIH support summary

Four things.

1. Attached please find the paper we sent to Caya et al last week.
2. I have asked Alan Guttmacher and Rose Higgins from NICHD to join our 315 call.
3. I have reattached the bullets that we sent earlier for completeness
4. I wanted to respond to the issue that Jerry raised about how (b)(5)

(b)(5)

(b)(5) Rationale follows.

(b)(5)

Talk to you at 3:15

From: Lewis-Evans, Amanda
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Lewis-Evans, Amanda
Subject: Review Requested: Notes from SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET
Date: Tuesday, April 30, 2013 12:37:58 PM
Attachments: SUPPORTSubcommitteeCal_04292013.docx

Hi Rose,

Please review and revise the attached notes as needed.

Thank you,

Amanda

From: Gabrio, Jenna
Sent: Thursday, April 25, 2013 11:35 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; Yvonne Vaucher; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; Becky Brazeel; 'Brenda Vecchio'; Cunningham, Meg; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET

Dear all,

Thank you all for your quick responses. Please find the call details below and remember that the participant passcode has recently been updated.

The SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in non-enrolled eligible babies has been schedule for:

Monday, 4/29
3:00pm ET

Dial:
Within the USA
(b)(6)

or

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abbot, Michele and Yvonne will be unable to join.

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Wednesday, April 24, 2013 9:14 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.

Please provide your availability for the following dates on the Doodle poll (http://www.doodle.com/48dpg9qq6f8peq8f):

4/25, Th
4/26, F

4/29, M
4/30, Tu
5/1, W
5/2, Th
5/3, F

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

SUPPORT Subcommittee Call
April 29, 2013

Participants: Kurt Schibler, Neil Finer, Wally Carlo, Jon Tyson, , Brad Yoder, Miriam Peralta, Wade Rich, Abbot Laptook
NICHD: Rose Higgins, Stephanie Archer
Data Coordinating Center: Kris Zaterka-Baxter, Amanda Lewis-Evans, Marie Gantz, Dennis Wallace, Abhik Das

---

Secondary Analysis

- The call participants agreed that the proposed secondary evaluation of whether treatment group affected risk-adjusted mortality in the comparison of risk among trial participants to comparison of risk in eligible individuals not enrolled will be deferred and will not be conducted at this time.

Action Plans

- No further action at this time.

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; "Bell, Edward (Pediatrics)"
Cc: "mgantz@rti.org"
Subject: RE: FW: SUPPORT analysis idea
Date: Tuesday, April 30, 2013 11:15:54 AM
Attachments: ROP ver 6.0 (03-28-2013) changesaccepted.docx

Here is the most recent draft. The Discussion is very preliminary.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 30, 2013 10:07 AM
To: Wally Carlo, M.D.; 'Bell, Edward (Pediatrics)'
Subject: RE: FW: SUPPORT analysis idea

Sure – send me the most recent draft and I can send for vote

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 11:03 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Bell, Edward (Pediatrics)'
Subject: RE: FW: SUPPORT analysis idea

Rose and Neil:

Can we ask the subcommittee to share the draft of the paper with Jack? He is always so helpful. He

emailed me about this when I presented at PAS to ROP prediction work.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 30, 2013 9:58 AM
To: 'Bell, Edward (Pediatrics)'
Cc: Wally Carlo, M.D.
Subject: RE: FW: SUPPORT analysis idea

Mine bounced also – I sent to Wade Rich who was able to forward

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, April 30, 2013 10:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo
Subject: FW: FW: SUPPORT analysis idea

The message bounced back twice from Neil's e-mail (nfiner@ucsd.edu). This address worked last week. Does he have another e-mail address?
Thanks,
Ed

From: Microsoft Outlook [mailto:MicrosoftExchange329e71ec88ae4615bbc36ab6ce41109e@uiowa.edu]
Sent: Tuesday, April 30, 2013 9:53 AM

To: Bell, Edward (Pediatrics)
Subject: Undeliverable: FW: SUPPORT analysis idea

Delivery has failed to these recipients or groups:

Finer, Neil
A problem occurred during the delivery of this message to this e-mail address. Try sending this message again. If the problem continues, please contact your helpdesk.

The following organization rejected your message: iport-c2-in.ucsd.edu.

Diagnostic information for administrators:

Generating server: HC-EDGE2.healthcare.uiowa.edu

nfiner@ucsd.edu
iport-c2-in.ucsd.edu #<iport-c2-in.ucsd.edu #5.0.0 smtp;550 #5.1.0 Address rejected.> #SMTP#

Original message headers:

Received: from HC-HUB2.healthcare.uiowa.edu (129.255.112.195) by
HC-EDGE2.healthcare.uiowa.edu (129.255.126.23) with Microsoft SMTP Server
(TLS) id 14.3.123.3; Tue, 30 Apr 2013 09:53:17 -0500
Received: from hc-mailboxc1-n4.healthcare.uiowa.edu ([169.254.4.67]) by
HC-HUB2.healthcare.uiowa.edu ([129.255.112.195]) with mapi id 14.03.0123.003;
Tue, 30 Apr 2013 09:53:18 -0500
From: "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu>
To: "Finer, Neil" <nfiner@ucsd.edu>
Subject: FW: SUPPORT analysis idea
Thread-Topic: SUPPORT analysis idea
Thread-Index: Ac5Fn4Hw0eqz96z7TQORPyfcQDewHQAEc87gAABEohA=
Date: Tue, 30 Apr 2013 14:53:18 +0000
Message-ID: <3667D4E8F9E42445B510D1823965B9FF04FAF92C@hc-mailboxc1-n4.healthcare.uiowa.edu>
References: <3667D4E8F9E42445B510D1823965B9FF04FAF55D@hc-mailboxc1-n4.healthcare.uiowa.edu>

Accept-Language: en-US
Content-Language: en-US
X-MS-Has-Attach: yes
X-MS-TNEF-Correlator:
x-originating-ip: [172.26.0.1]
x-my-disclaimer: ready
Content-Type: multipart/mixed;
boundary="_004_3667D4E8F9E42445B510D1823965B9FF04FAF92Chcmailboxc1n4he_"
MIME-Version: 1.0
Return-Path: edward-bell@uiowa.edu

ROP Secondary ver 6.0
(03/28/2013)

Oxygen Saturations and Retinopathy of Prematurity in Extremely Preterm Infants

Marie G. Gantz, Ph.D.[1]; Waldemar A. Carlo, M.D.[2]; Neil N. Finer, M.D.[3]; Wade Rich, RRT[3]; Roger G. Faix, M.D.[4]; Bradley Yoder, M.D.[4]; Michele C. Walsh, M.D., M.S.[5]; Nancy Newman, R.N.[5]; Abbot Laptook, M.D.[6]; Kurt Schibler, M.D.[7]; Abhik Das, Ph.D.[8]; Rosemary D. Higgins, M.D.[9]

[1]RTI International, Research Triangle Park, North Carolina; [2]University of Alabama at Birmingham, Birmingham, Alabama; [3]University of California, San Diego, San Diego, California; [4]University of Utah, Salt Lake City, Utah; [5]Case Western Reserve University, Cleveland, Ohio; [6]Women and Infants Hospital of Rhode Island, Providence, Rhode Island; [7]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [8]RTI, Rockville, Maryland; [9]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Corresponding author and reprints:

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Birmingham, AL 35233-7335

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Comment [WC1]: Marie: You can change this to you. It does not matter.

Word count

Abstract: 250

Text: 2,284

Short title: Oxygen saturations and retinopathy of prematurity

Abbreviations: ROP = Retinopathy of prematurity

Keywords: Infant Mortality, Newborn, Infant, Oximetry, Oxygen/administration & dosage, Oxygen Inhalation Therapy/adverse effects

ABSTRACT

Comment [MG2]: Now 250 words

Background

In the SUPPORT trial, severe retinopathy of prematurity (ROP) among survivors was decreased from 17.9% to 8.6% with oxygen saturation targets of 85-89% vs. 91-95% (relative risk 0.52, 95% confidence interval (CI) 0.37 - 0.73).

Objective

To identify oxygen saturation levels associated with severe ROP.

Methods

Data on oxygen saturation and supplementation were collected up to 36 weeks post menstrual age or severe ROP determination for infants of 24 – 27 weeks gestational age enrolled in SUPPORT. Logistic regression models were created to predict severe ROP based on perinatal risk factors, percent of days receiving supplemental oxygen, and percent of time spent in various saturation ranges while on supplemental oxygen.

Results

Comment [WC3]: I am concerned that the data may not support our emphasis on days on oxygen other than it is the only variable in the log reg model that can be modified by the health care worker but that is not clear in the results.

Forty-five percent (60/132) of survivors with severe ROP received supplemental oxygen every day compared to 17% (142/852) of survivors without severe ROP, $p < 0.001$. In logistic regression modeling, percentage of days on supplemental oxygen (odds ratio (OR) for a 5% increase 1.14, 95% CI 1.06 – 1.22), center, lower gestational age, small for gestational age ($<10^{th}$ percentile), severe illness ($FiO_2 > 0.4$ and on ventilator for > 8 consecutive hours in the first 14 days of life), and late onset sepsis or meningitis were predictors of severe ROP. Among infants with supplemental oxygen every day (N = 202), more time with a saturation of 100% was associated with severe ROP (OR for a 5% increase 2.71, 95% CI 1.05, 6.96).

Conclusions

Among infants who survived to discharge, those with severe ROP spent significantly more time on oxygen supplementation.

Comment [WC4]: I like these sentences very much but as they are speculation, I think it is best to move to the Discussion. I put it as the last two sentences.

Introduction

Retinopathy of prematurity (ROP) is an important cause of blindness and other visual disabilities in preterm infants. The occurrence of ROP is indirectly proportional to gestational age, but high oxygen exposure has been associated with increased risk of retinopathy. The incidence of ROP increased with exposure to unrestricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.[1] However, the resultant practice of restricting oxygen supplementation, usually to no more than 50% inspired oxygen concentration, based on the oxygen restriction trials in the 1950s was estimated to result in an excess of 16 deaths per case of blindness prevented.[2]

Comment [WC5]: Need to get reference. I think it is in the SUPPORT paper

MG: Added reference.

In the SUPPORT trial, 1316 infants born at gestational ages of 24 0/7 weeks to 27 6/7 weeks between February 2005 and February 2009 were randomized to oxygen saturation target ranges of either 85-89% or 91-95%. Severe ROP among survivors was decreased in the lower (85-89%) oxygen saturation target group compared to the higher (91-95%) oxygen saturation target group (relative risk 0.52, 95% confidence interval 0.37, 0.73, $p < 0.001$, number needed to treat = 11),[3] and the duration of oxygen supplementation among survivors was shorter. However, mortality was increased in the lower oxygen saturation group. Two similarly designed trials have been terminated prematurely due to similar mortality findings.[4]

Comment [WC6]: I thought only the Brit trial ended early.

MG: Both the UK and Australian BOOST II trials were ended early.

More recent data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of ROP relative to low normal levels.[5-8] In three pre-post design studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.[7,11,12] Although a

multicenter observational study did not report a significant association between PaO_2 levels and retinopathy[9], a single center cohort study using transcutaneous oxygen monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels $\geq$ 80 mmHg.[10] While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ROP, concerns remain about the safety of low oxygen saturation targets.

Thus, there is a need to determine the oxygen saturation levels that were associated with severe ROP among survivors in the SUPPORT trial to assist in the selection of safe oxygen saturation targets that optimize survival but do not increase the risk of severe ROP. This is very important because the actual oxygen saturation levels achieved differed from the targets aimed for in SUPPORT, and the oxygen saturations while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably. Furthermore, it is likely that the overall duration of oxygen supplementation and other demographic characteristics and neonatal morbidities are associated with a higher risk of severe ROP. This study tests the hypothesis that there is a range of oxygen saturation levels that increases the risk of severe ROP independent of other baseline characteristics. It also tests the hypothesis that demographic characteristics, gestational age, duration of oxygen exposure, and neonatal morbidities will be associated with a higher risk of severe ROP independent of other characteristics.

Methods

This was a secondary analysis of the data from the oxygen saturation SUPPORT Trial.[3]

Study Assessments and Data Collection

Determination of Severe ROP

All surviving infants were followed by ophthalmologists trained in the diagnosis of ROP. Examinations began by 33 weeks of postmenstrual age (PMA) and continued until the severe ROP outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group[13,14]) was diagnosed if any of the following findings were present: in zone 1, stage 3 ROP, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; in zone 2, plus disease with stage 2 ROP or plus disease with stage 3 ROP. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. Severe retinopathy was defined as threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy. [3]

Comment [MG7]: This was copied directly from the original NEJM paper

Respiratory Support

Respiratory support data, including mode of support and FiO_2, were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life, and once a day from 15 days of life through 36 weeks PMA or death, transfer or discharge. After February 2006, respiratory support data were collected every two hours for the first 14 days of life, and every 6 hours thereafter through 36 weeks PMA or death, transfer or discharge.

Pulse Oximeter Data

Oxygen saturation data sampled every 10 seconds were collected while infants were receiving oxygen supplementation. Use of the study pulse oximeters was discontinued at 36 weeks PMA or when the infant had been without respiratory support for three days, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks PMA, the study oximeter was placed back on the infant.

Masking of treatment assignment was maintained using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, saturation values in the correct target range were displayed as 88-92% (a maximum variation of 3% from the actual value). Display, not actual, oxygen saturation values were recorded; thus, the data required transformation to actual saturation values prior to analysis. For some saturation values there was not a one-to-one correspondence between display and actual values (84-85% and 93-96% in the low target group, 84-87% and 95-96% in the high target group). In these ranges, the number of seconds spent at each saturation value was interpolated using a quadratic curve, ensuring that the total number of seconds was conserved (ref BOOST II UK group for method?). In cases where this method resulted in interpolation of a negative number of seconds, cubic Hermite interpolation, constrained to produce non-negative results, was used instead.

Oxygen saturations could only be targeted to assigned ranges while the infant was receiving supplemental oxygen. Furthermore, previous unpublished analyses of the SUPPORT pulse oximeter data revealed that infants spent more time with oxygen saturations of 97-100% on days when they did not receive supplemental oxygen compared to days on oxygen. For these reasons, this analysis included only those pulse oximeter data collected during oxygen supplementation. We considered the oximeter data to be for time on supplemental oxygen if the infant was receiving oxygen at the closest time point for which respiratory support data were collected on study forms. Pulse oximeter data from dates after the eye exam at which the ROP outcome (either severe ROP or resolution) was determined were excluded from this analysis.

Statistical Methods

Comment [WC8]: I put this sentence first as it was the hypothesis

The percent of time spent at various oxygen saturation (SpO_2) values while receiving supplemental oxygen was compared graphically for infants with and without severe ROP. The relationship between severe ROP and the amount of time spent on supplemental oxygen was explored using descriptive statistics. Both the total number of days and overall percent of days spent on supplemental oxygen up to 36 weeks PMA or severe ROP outcome determination were examined, and the Pearson correlation between the two measures was assessed.

Exploratory multivariate analysis was used to assess the relationship between severe ROP and the percent of time spent at various SpO_2 values while on oxygen supplementation. The result of this analysis was a linear combination of the percentages of time at each SpO_2 value that best discriminated between infants with and without severe ROP. This discriminant function was interpreted by measuring the correlation between it and the original percentages of time at each SpO_2 value.

Oxygen saturation values found to be most highly associated with severe ROP in the multivariate analyses were included as covariates in logistic regression models predicting severe ROP based on the amount of time spent on supplemental oxygen (both the number of days and percent of days on oxygen were evaluated as potential predictors) and demographic and neonatal characteristics. Selection of demographic and neonatal characteristics was based on possible association with ROP and included clinical center, gender, race/ethnicity, gestational age (GA), small for gestational age ($<10^{th}$ percentile) (SGA), any receipt of antenatal steroids, severe illness defined as $FiO_2 > 0.4$ and being on a ventilator for > 8 consecutive hours in the first 14 days of life, time weighted CO_2 in the first 14 days of life (as an indicator of severity of lung disease), periventricular leukomalacia (PVL), grade III or IV intraventricular hemorrhage (severe IVH), necrotizing enterocolitis (NEC), and late onset

sepsis/meningitis. For PVL, severe IVH, NEC, and late onset sepsis/meningitis, only morbidities reported before the date of severe ROP outcome determination were included.

Separate analyses were conducted for all infants who survived to discharge and had a severe ROP outcome determined, and for the subset of infants who received supplemental oxygen every day up to 36 weeks PMA or severe ROP outcome determination. Due to the reduced number of infants available for the second analysis, the logistic regression model was reduced using backward selection and only predictors that were statistically significant at the $p<0.05$ level were retained in the final model.

Results

Of the 984 infants who survived to discharge and had the severe ROP outcome determined, 132 (13%) had severe ROP. Ninety-five percent (125/132) of those with severe ROP received supplemental oxygen on at least half of the days prior to 36 weeks PMA or severe ROP outcome determination, compared to 64% (541/852) of infants without severe ROP. Forty-five percent (60/132) of the infants with severe ROP received supplemented oxygen every day compared to 17% (142/852) of the infants without severe ROP, $p < 0.001$. The median number of days on which oxygen was received was 67 for infants with severe ROP (interquartile range (IQR) 54-74) and 43.5 for infants without severe ROP (IQR 18-63). The correlation between number of days and percent of days with supplemental oxygen was high (0.82 among those with severe ROP, and 0.94 among those without severe ROP).

Comment [MG9]: Need to include test in methods.

Ninety-five percent (932/984) of SUPPORT infants who survived to discharge and had a ROP outcome determined had oxygen saturation data available. Figure 1 compares the percent of time spent at various SpO_2 values while receiving supplemental oxygen for infants with and without severe ROP. In

multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with SpO_2 values less than 80% (correlations between discriminant function and original predictors were >0.5). In logistic regression analysis adjusted for other risk factors, percent of days on supplemental oxygen prior to 36 weeks PMA or severe ROP outcome determination was predictive of severe ROP (odds ratio (OR) for a 5% increase 1.14, 95% CI 1.06, 1.22, p<0.001), but percent of time while on supplemental oxygen with SpO_2 <80% was not (OR 1.01, 95% CI 0.93, 1.09, p=0.89). Other significant predictors were clinical center, GA, SGA, severe illness, and late-onset sepsis or meningitis (Table 1). When number of days was substituted for percent of days receiving supplemental oxygen, it was not a significant predictor (OR 1.02, 95% CI 0.999, 1.03, p=0.06), but otherwise model results were similar.

Figure 2 compares the percent of time spent at various SpO_2 values while receiving supplemental oxygen for infants with and without severe ROP among the 202 infants who received supplemental oxygen every day up to 36 weeks PMA or severe ROP outcome determination.

In multivariate analysis of this subset of infants, severe ROP was most associated with a greater percentage of time with an SpO_2 of 100% (correlation of 0.35 between discriminant function and original predictor). This variable was also significant in the logistic regression model to predict severe ROP (OR for a 5% increase 2.71, 95% CI 1.05, 6.96, p=0.04). Other significant predictors were male gender, GA, SGA, severe illness, and late-onset sepsis or meningitis (Table 2). Number of days receiving supplemental oxygen was not a significant predictor of severe ROP in this subgroup.

Discussion (last paragraph, pending first part)

The study results are limited as some oximeter data values needed to be interpolated due to the lack of a one-to-one match between the skewed SpO_2 values displayed by the oximeters and actual saturations. However, this did not affect SpO_2 values below 84% or above 96% which were of greatest interest in this analysis. Another limitation is that oximeter data for time on supplemental oxygen were identified based on the closest time point at which respiratory support data were captured on study forms. As respiratory support data were not continuously reported, it is possible that some oximeter data for times when the infants were not actually receiving supplemental oxygen were included in this analysis. Based on previous unpublished analyses of the oximeter data, the most likely impact of including time not on oxygen support would be an increase in oximeter readings with oxygen saturations near 100%.

In conclusion, a greater proportion of days with receipt of supplemental oxygen prior to 36 weeks post-menstrual age is one of the strongest predictors of severe ROP. Severe pulmonary disease, late-onset sepsis or meningitis, PVL, SGA, lower GA, and center were other predictors of severe ROP. Among infants who received supplemental oxygen every day up to 36 weeks PMA or severe ROP outcome determination, less time spent on oxygen with a SpO_2 of 100% was associated with a decrease in severe ROP. These results support the concept that infants with prolonged oxygen need are at high risk for severe ROP. This effect is larger than the effects of time spent in specific oxygen saturation ranges.

Comment [MG10]: Could it be that the increased survival in the High group resulted in (a) more infants who were sicker and could have been at increased risk for morbidities in the High group and/or (b) survivors in the Low group being stronger infants, less at risk for morbidities?

Comment [WC11]: I think we should highlight the main results/interpretation before going into limitations.

MG- I agree. I added the limitations because I did not want to forget them.

Comment [WC12]: I have to read more papers on the subject to put our results in perspective of the most pertinent literature.

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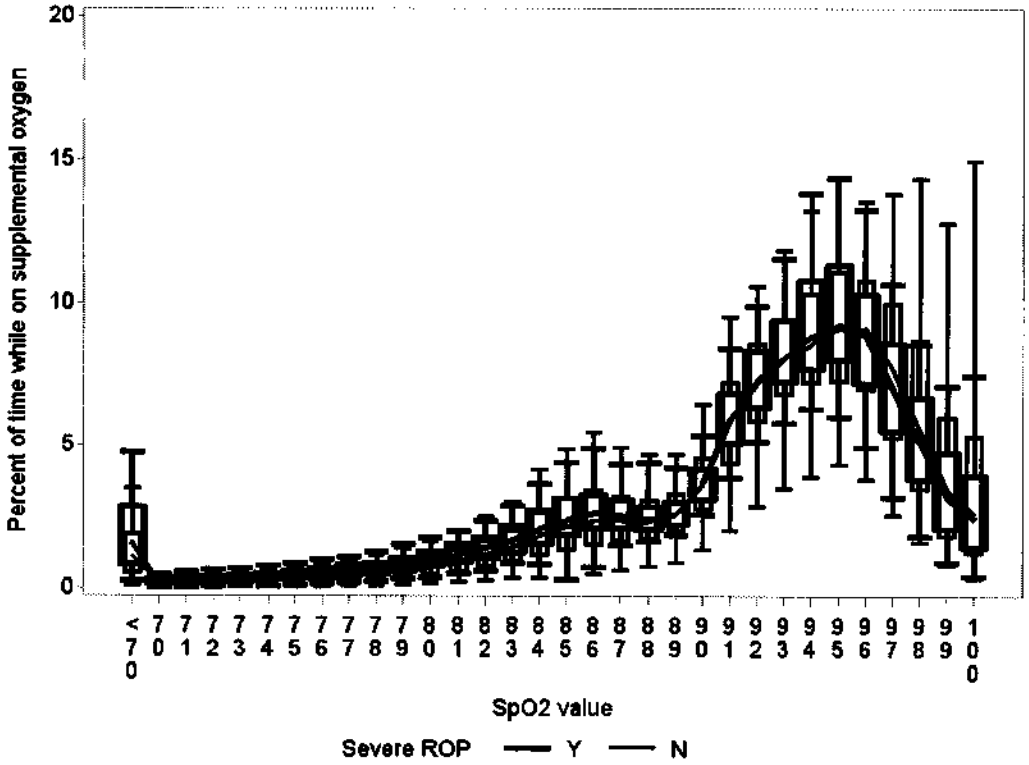
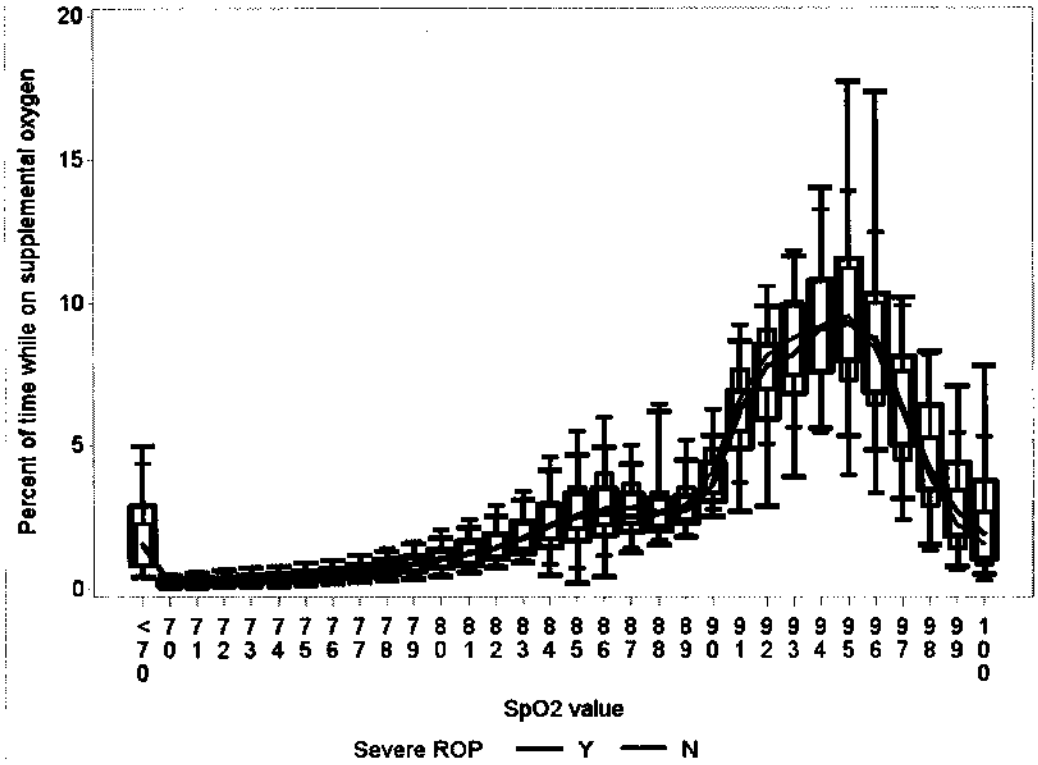
Figure 1. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks PMA or severe ROP outcome determination



Boxes represent 25th to 75th percentiles. Whiskers represent 5th to 95th percentiles. Lines connecting the boxes represent medians.

Figure 2. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks PMA or severe ROP outcome determination for infants who received oxygen each day



Boxes represent 25th to 75th percentiles. Whiskers represent 5th to 95th percentiles. Lines connecting the boxes represent medians.

Comment [WC13]: A bit crowded but I think it is the best way to report the data. Could we add symbols to identify significant differences at each SPO2 value using univariate analyses?

MG: I will look into indicating significant differences.

Table 1. Model predicting severe ROP among survivors to discharge

	Adjusted OR	Adjusted 95% CI	P value
Percent of days on oxygen (unit=5% increase)	1.14	(1.06, 1.22)	<0.001
Percent of time with SpO2<80% while on oxygen	1.01	(0.93, 1.09)	0.89
Severe illness	3.50	(2.05, 5.97)	<0.001
Time weighted CO_2 in the first 14 days of life	0.99	(0.95, 1.03)	0.60
PVL	2.09	(1.83, 5.28)	0.12
IVH grade 3-4	1.10	(0.53, 2.28)	0.79
NEC	1.11	(0.53, 2.30)	0.78
Late-onset sepsis or meningitis	2.11	(1.31, 3.39)	0.002
Any antenatal steroids	0.49	(0.13, 1.92)	0.31
Male	1.23	(0.77, 1.96)	0.38
Gestational age (weeks)	0.49	(0.38, 0.63)	<0.001
Small for gestational age	2.38	(1.04, 5.47)	0.04
Race/ethnicity			0.21
Non-Hispanic Black vs. Non-Hispanic White	0.54	(0.30, 0.99)	
Hispanic vs. Non-Hispanic White	0.89	(0.43, 1.84)	
Other vs. Non-Hispanic White	1.16	(0.35, 3.82)	
Center			0.15

Table 2. Model predicting severe ROP among survivors to discharge who received supplemental oxygen every day to 36 weeks PMA or severe ROP outcome determination

	Adjusted OR	Adjusted 95% CI	P value
Percent of time with SpO_2=100% while on oxygen (unit=5% increase)	2.71	(1.05, 6.96)	0.04
Severe illness	2.48	(1.04, 5.90)	0.04
Late-onset sepsis or meningitis	2.31	(1.13, 4.72)	0.02
Male	2.38	(1.13, 5.00)	0.02
Gestational age (weeks)	0.45	(0.30, 0.68)	<0.001
Small for gestational age	4.06	(1.35, 12.23)	0.01

From: Bell, Edward (Pediatrics)
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: SUPPORT analysis idea
Date: Tuesday, April 30, 2013 11:07:05 AM

Good idea. Especially since Jack just shared his unpublished manuscript with us.

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 30, 2013 10:03 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward (Pediatrics)
Subject: RE: FW: SUPPORT analysis idea

Rose and Neil:

Can we ask the subcommittee to share the draft of the paper with Jack? He is always so helpful. He emailed me about this when I presented at PAS to ROP prediction work.

Wally

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 30, 2013 9:58 AM
To: 'Bell, Edward (Pediatrics)'
Cc: Wally Carlo, M.D.
Subject: RE: FW: SUPPORT analysis idea

Mine bounced also – I sent to Wade Rich who was able to forward

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From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, April 30, 2013 10:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo
Subject: FW: FW: SUPPORT analysis idea

The message bounced back twice from Neil's e-mail (nfiner@ucsd.edu). This address worked last week. Does he have another e-mail address?
Thanks,
Ed

From: Microsoft Outlook [mailto:MicrosoftExchange329e71ec88ae4615bbc36ab6ce41109e@uiowa.edu]
Sent: Tuesday, April 30, 2013 9:53 AM
To: Bell, Edward (Pediatrics)
Subject: Undeliverable: FW: SUPPORT analysis idea

Delivery has failed to these recipients or groups:

Finer, Neil
A problem occurred during the delivery of this message to this e-mail address. Try sending this message again. If the problem continues, please contact your helpdesk.

The following organization rejected your message: iport-c2-in.ucsd.edu.

Diagnostic information for administrators:

Generating server: HC-EDGE2.healthcare.uiowa.edu

nfiner@ucsd.edu
iport-c2-in.ucsd.edu #<iport-c2-in.ucsd.edu #5.0.0 smtp;550 #5.1.0 Address rejected.> #SMTP#

Original message headers:

Received: from HC-HUB2.healthcare.uiowa.edu (129.255.112.195) by
HC-EDGE2.healthcare.uiowa.edu (129.255.126.23) with Microsoft SMTP Server
(TLS) id 14.3.123.3; Tue, 30 Apr 2013 09:53:17 -0500
Received: from hc-mailboxc1-n4.healthcare.uiowa.edu ([169.254.4.67]) by
HC-HUB2.healthcare.uiowa.edu ([129.255.112.195]) with mapi id 14.03.0123.003;
Tue, 30 Apr 2013 09:53:18 -0500
From: "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu>
To: "Finer, Neil" <nfiner@ucsd.edu>
Subject: FW: SUPPORT analysis idea
Thread-Topic: SUPPORT analysis idea
Thread-Index: Ac5Fn4Hw0eqz96z7TQORPyfcQDewHQAEc87gAABEohA=
Date: Tue, 30 Apr 2013 14:53:18 +0000
Message-ID: <3667D4E8F9E42445B510D1823965B9FF04FAF92C@hc-mailboxc1-

n4.healthcare.uiowa.edu>
References: <3667D4E8F9E42445B510D1823965B9FF04FAF55D@hc-mailboxc1-n4.healthcare.uiowa.edu>

Accept-Language: en-US
Content-Language: en-US
X-MS-Has-Attach: yes
X-MS-TNEF-Correlator:
x-originating-ip: [172.26.0.1]
x-my-disclaimer: ready
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boundary="_004_3667D4E8F9E42445B510D1823965B9FF04FAF92Chcmailboxc1n4he_"
MIME-Version: 1.0
Return-Path: edward-bell@uiowa.edu

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From: Bell, Edward (Pediatrics)
To: Wally Carlo; Finer, Neil
Cc: Sinclair, Jack; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT analysis idea
Date: Tuesday, April 30, 2013 10:51:21 AM
Attachments: Marcucci-Sinclair manuscript Mar302013.doc

Dear Wally and Neil,

Jack Sinclair is interested in exploring use of the SUPPORT database develop clinical prediction guides applicable in the first 3 days after birth to predict individualized risks for death, severe ROP, and BPD. I think this might be an important first step toward learning how to set oxygen saturation targets that are personalized for individual patients. Jack gave me permission to share the attached unpublished manuscript with you – in confidence, of course.

See Jack's additional 2 comments about this:

i) There is a potential to utilize existing clinical prediction guides (CPGs), as well as develop new CPGs nested in the SUPPORT database, in order to develop individualized predictions of treatment effect. My latest survey of existing validated CPGs catalogued in EvidenceUpdates indicates that in fact there is none at present for individualizing the predicted risk for severe ROP in this population. But that could change at any moment. There may be existing validated CPGs that are applicable to individualized prediction of death or BPD in this population (for example, Laughon). So potentially we would be interested in the use of the SUPPORT database not only for the development of new CPGs, but also for the application of CPGs, existing or newly developed, in generating individualized predictions of treatment effect.

ii) In this project, we welcome and, indeed, solicit the participation of SUPPORT investigators and statisticians who would be interested in collaborating.

If you agree this idea is worth exploring, I will ask Rose to seek SC approval to share the SUPPORT data forms with Jack and his colleague and coauthor Maura Marcucci at McMaster, so they can see exactly which data elements are available in the SUPPORT database.

Thanks,
Ed

Confidential: do not distribute. Submitted for publication April 2013

A generalized model for individualizing a treatment recommendation based on group-level evidence from randomized clinical trials

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Key Words: *Clinical Decision-Making, Clinical Prediction Guides, Treatment Benefit, Treatment Harm, Patient Values*

Word count: 4039

Abstract

Objectives. Randomized controlled trials report group-level treatment effects. However, an individual patient confronting a treatment decision needs to know whether that person's expected treatment benefit will exceed the expected treatment harm. We describe a flexible model for individualizing a treatment decision. It uses group-level treatment effects from randomized trials and individualized estimates of absolute treatment benefit and harm generated from clinical prediction guides.

Methods. We constructed models that estimate the size of individualized absolute risk reduction for the target outcome that is required to offset individualized absolute risk increase for the treatment harm. Inputs to the model include estimates for individualized predicted absolute treatment benefit and harm, and the relative value assigned by the patient to harm/benefit. A decision rule recommends treatment when the patient's predicted benefit exceeds the predicted harm, value-adjusted. We also derived expressions for the maximum treatment harm, or the maximum relative value for harm/benefit, above which treatment would not be recommended.

Results. We developed a simple model, applicable to treatments causing one kind of benefit and one kind of harm. The individualized absolute risk reduction required to justify treatment was expressed as Required $ARR_{target(i)}=ARI_{harm(i)}*RV_{harm/target(i)}$. A complex model was also developed, applicable to treatments causing multiple kinds of benefits and/or harms. We demonstrated the applicability of the models to treatments tested in superiority trials (either placebo control or active control, either fixed harm or variable harm), and non-inferiority trials.

Conclusions. Individualized treatment recommendations can be derived using a model that applies clinical prediction guides to the results of randomized trials in order to identify which individual patients are likely to derive a clinically important benefit from the treatment. The resulting individualized treatment recommendations require

validation by comparison of the results of individualized prediction-based treatment with strategies of treat all or treat none.

What is already known on this topic

- RCTs provide group-level relative estimates of the beneficial and harmful effects of a treatment. However, the absolute size of those effects may vary across individuals according their baseline risk
- A model has previously been described to individualize results of superiority placebo-control trials in a variable benefit/fixed harm setting, using Clinical Prediction Guides to individualize the predicted risk of the target event in the trial's control group

What this study adds

- We provide a generalized model to individualize treatment recommendations. We start from the definition of the Clinically Important Difference: the size of treatment benefit that offsets the treatment harm, after adjusting for the patient's values
- The model applies to variable benefit and fixed or variable harm, and to superiority (placebo and active control) and non-inferiority trials. It can accommodate more than one kind of benefit and/or harm. Clinical Prediction Guides are used to individualize the predicted risk of the target event and of the harm in the trial's control group
- The model allows the calculation of an individual's maximum absolute risk increase for the treatment harm, or the maximum relative value for harm/benefit, above which the decision to treat would be overturned.

Introduction

For questions of treatment and prevention, randomized controlled trials (RCTs) provide the most valid evidence concerning the benefits and, often, the harms of the intervention. However, RCTs typically report only group-level results, whereas treatment effects may depend importantly on characteristics of individual patients.

A clinical prediction guide (CPG)[1-3] uses patient-specific risk data to predict the level of risk for a clinical outcome of interest for an individual patient. CPGs applied to participants in clinical trials can predict the individual patient's level of risk at trial entry (baseline risk) for the target outcome at which the treatment is directed, and also for harm caused by the treatment. If the relative risk reduction for the target outcome (or relative risk increase for the harm) is constant across the range of baseline risk, then absolute treatment effects can be predicted in individual patients: absolute risk reduction (ARR) for the target outcome (the treatment benefit) and absolute risk increase (ARI) for the treatment harm.

But what size of ARR for the target benefit is sufficiently large to justify acceptance of a treatment that carries a potential for both benefit and harm? That depends on the frequency of the harm caused by treatment, and the relative importance of the harm compared to the benefit. The size of treatment benefit that is large enough to offset the treatment harm is the patient's clinically important difference (CID).

The concept of the CID has been incorporated in several prior formulations: the threshold ARR (inverted, the threshold number needed to treat[4]), the threshold for agreeing with treatment,[5] the decision threshold (inverted, the number willing to treat).[6] Each of these constructs embodies the concept that for treatment to be justified, the predicted treatment benefit must exceed the predicted harm for that individual.

Absolute treatment benefits vary directly with the baseline risk for the target benefit: for an effective treatment, the higher the baseline risk, the greater the predicted absolute benefit. When modeling absolute treatment effects across individuals, the assumed model usually has incorporated a variable benefit, but a *fixed* harm.[4-7] However, the absolute size of treatment harms may also vary across individuals, in which case a variable benefit/*variable* harm model would apply. The two models are illustrated in Figure 1.

The objectives of this report are: i) to derive an expression for the CID that is flexible and applicable to either fixed or variable treatment harm, and ii) to describe a generalized model for deriving a treatment recommendation based on the CID, using group-level estimates of treatment effects provided by RCTs and CPGs for prediction of individualized absolute treatment benefit and harm.

Methods

We define the CID as the size of benefit from the treatment that offsets the harm of the treatment. We define a benefit as the reduction of the occurrence of the target outcome, expressed as the negative outcome, e.g. death, rather than the positive outcome, e.g. survival. When the benefit is defined categorically, the CID is the required absolute risk reduction for the target outcome (ARR_{target}) obtained with the treatment compared to the control. The control can be no treatment (or placebo) or an active control. The model contains parameters for the predicted individualized treatment benefit, the predicted individualized treatment harm, and the patient's values. The model accommodates more than one kind of benefit and more than one kind of harm. No economic cost, either direct or indirect, is included in the model.

When applied to individualize a treatment recommendation, the model provides an individualized required ARR_{target}. A decision rule recommends the treatment when the patient's predicted ARR_{target} is greater than her required ARR_{target}.

Data requirements

Table 1 summarizes the required quantities for entry into the model, distinguishing between group-level measures and individual-level predictions.

Group-level quantities. Most of the shown group-level quantities are used to generate individualized estimates. For treatment benefits, the required group-level measure is the relative risk reduction. The data source can be a meta-analysis of large RCTs or a single large RCT. The required group-level quantities for the harms depend on the type of harm, fixed or variable. For fixed harms, we use a group-level absolute quantity, the absolute risk increase (ARI_{harm}). For variable harms, we use a group-level relative quantity, the relative risk increase (RRI_{harm}). Whether fixed or variable, the estimate of the treatment effect for harms comes from a meta-analysis of large RCTs, a single large

RCT or best available observational evidence. Values are entered as relative value (RV) of the harm compared to the target benefit. A group-level $RV_{harm/target}$ can be derived from formal utility-based analyses, patient groups, or expert opinion.

Individual-level quantities. The individualized treatment benefit is expressed as absolute risk reduction ($ARR_{target(i)}$). The individualized treatment harm is expressed as absolute risk increase ($ARI_{harm(i)}$). For baseline risk (BLR) we mean the risk in the reference group (the control arm in the trial), whether it is represented by patients on no treatment or placebo or by patients on an existing treatment. **Table 2** summarizes the role of CPGs in individualizing predicted treatment benefits and harms.

- Benefits modeling. The model allows the predicted $ARR_{target(i)}$ to increase for increasing baseline risks for the target outcome ($BLR_{target(i)}$), according to the equation: predicted $ARR_{target(i)}=RRR_{target}*BLR_{target(i)}$. The group-level RRR_{target} is assumed to be constant across different baseline risks. The $BLR_{target(i)}$ for the target benefit is estimable using a validated CPG.
- Harms modeling. In the case of fixed harm, the group-level estimate ($ARI_{harm(trial)}$) is used for the predicted $ARI_{harm(i)}$. No CPG is needed to predict an individualized harm. When the receipt of the treatment per se is modeled as fixed harm (as with risk/discomfort), that harm is experienced by every treated patient, so the $ARI_{harm(trial)}$ for the harm is constantly equal to 1.0 (100%). In the case of variable harm across subjects, the predicted $ARI_{harm(i)}$ is calculated multiplying the group-level RRI_{harm} by the individualized baseline risk for that harm ($BLR_{harm(i)}$). The group-level RRI_{harm} is assumed constant across different baseline risks. The $BLR_{harm(i)}$ can be estimated using a validated CPG.
- Values modeling. An individual RV ($RV_{harm/target(i)}$) assigned by the patient enters the model. We recognize that a $RV_{harm/target(i)}$ may not be ascertained reliably. Therefore we modeled a range of RVs centered on a group-level RV.

When more than one benefit and/or more than one harm is included, for each benefit and harm the specific $ARR_i/ARI_i/RV_i$ is separately calculated or assigned as above.

Construction of models for individualizing a treatment recommendation

We constructed two models: a simple model where there is one kind of treatment benefit and one kind of treatment harm; and a complex model where there is more than one kind of benefit and/or more than one kind of harm. In both cases, the model equation is solved for the required $ARR_{target(i)}$ to offset the treatment harm(s), given the predicted $ARI_{harm(i)}$ and $RV_{harm/target(i)}$. The same basic equation can then be used to calculate:

i) the maximum $ARI_{harm(i)}$ above which treatment would not be justified, given the predicted $ARR_{target(i)}$ and $RV_{harm/target(i)}$

ii) the maximum $RV_{harm/target(i)}$ above which treatment would not be justified, given the predicted $ARR_{target(i)}$ and $ARI_{harm(i)}$.

Results

1. Algebraic solution to the model

We derived the following equations to describe the model (see **Appendix** for algebraic details)

1.1. Simple model: one kind of treatment benefit, one kind of treatment harm (Appendix, §1)

1.1.2. Required $ARR_{target(i)}$

The required size of the ARR_{target} that offsets the treatment harm, value-adjusted, for the patient i, can be calculated as (Appendix, equations (1) and (2))

required $ARR_{target(i)} = ARI_{harm(i)} * RV_{harm/target(i)}$ (m_1)

The equation includes the particular condition of a fixed harm when ARI_{trial} can substitute for the ARI_i. When the treatment receipt is considered the harm, the ARI_{trial} is 1.0 and so the $ARR_{(target)i}$ is directly predictable from the $RV_{harm/target(i)}$ as

required $ARR_{target(i)} = RV_{harm/targe(i)}$ (m_2)

Decision rule. Both in case of fixed and in case of variable harm, the treatment would be justified for the patient i when

predicted $ARR_{target(i)}$ > required $ARR_{target(i)}$ (d_1)

1.1.3. Maximum $ARI_{harm(i)}$ and maximum $RV_{harm/target(i)}$

The maximum $ARI_{harm(i)}$ above which the treatment would not be justified for the patient i can be calculated as (Appendix, equations (1) and (3))

maximum $ARI_{harm(i)} = ARR_{target(i)} / RV_{harm/target(i)}$ (m_3)

Decision rule. The treatment would not be justified for the patient i when

predicted $ARI_{harm(i)}$ > maximum $ARI_{harm(i)}$, (d_2)

where the predicted $ARI_{harm(i)}$ can be fixed (=ARI_{trial}) or variable.

Similarly, the maximum $RV_{harm/target(i)}$ above which the treatment would not be justified for the patient i can be calculated as (Appendix, equations (1) and (4))

maximum $RV_{harm/target(i)} = ARR_{target(i)} / ARI_{harm(i)}$ (m_4)

Decision rule. The treatment would not be justified for the patient i when

patient's $RV_{harm/target(i)}$ > maximum $RV_{harm/target(i)}$ (d_3)

1.2. Complex model: multiple treatment benefits, multiple treatment harms (Appendix, § 2)

The model can be generalized to incorporate additional treatment benefits other than the reduction of the target outcome, and multiple harms. In this case, the required size of the ARR_{target}, value-adjusted, that offsets the treatment harms, and accounts for other treatment benefits, is calculated for the patient i as (Appendix, equations (5), (6) and (7))

required $ARR_{target(i)} = \sum_{(for\ j=1\ to\ k)} ARI_{harm(j)(i)} * RV_{(harm(j)/target)(i)} - \sum_{(for\ j=2\ to\ m)} ARR_{benefit(j)(i)} * RV_{(benefit(j)/target)(i)}$ (m_5)

where k is the number of treatment harms, m is the total number of treatment benefits, and the benefit(2) to benefit(m) are the benefits other than the target benefit. Every $RV_{(i)}$ is expressed as the value assigned to each outcome, prevented or caused by the treatment, compared with the value of the target benefit.

Decision rule. Similarly to the case of only one benefit and harm, the treatment would be justified for the patient i when

predicted $ARR_{target(i)}$ > required $ARR_{target(i)}$ (d_1)

The complex model can be used to predict the individualized maximum allowed ARI for a target harm and the maximum RV for the target benefit compared to a target harm, above which the treatment is not justified.

2. Applicability of the model

Theoretically, the model is applicable to every situation tackling the choice between two treatment strategies. Three examples are proposed to show the applicability of the model to individualize treatment recommendations: a superiority trial with variable benefit/*fixed* harm scenario; a superiority trial with variable benefit/*variable* harm scenario; and the case of non-inferiority trials.

2.1. Superiority trial: variable benefit, *fixed* harm. Rosuvastatin for primary prevention of cardiovascular events

The Justification for the Use of Statins in Prevention (JUPITER) trial[8] evaluated the effect of rosuvastatin vs placebo for reduction of cardiovascular events in apparently healthy men and women with LDL cholesterol levels <3.4 mmol/L and elevated high-sensitivity C-reactive protein. The primary outcome was a composite of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death. The group-level result showed a substantial relative benefit of rosuvastatin (hazard ratio 0.56, 95% CI 0.46, 0.69). This is equivalent to an RRR_{target} of 0.44 (95% CI 0.31, 0.54). Nevertheless, the individual's absolute benefit with rosuvastatin will vary according to her baseline risk (BLR_i). Validated CPGs exist to predict the baseline risk for cardiovascular events. The Framingham risk score,[9] for example, predicts the risk of cardiovascular events at 10 years combining risk factors such as age, gender, smoking, total and HDL cholesterol levels, systolic blood pressure, hypertension. Dorresteijn and

colleagues[6] used the group-level quantities provided by the JUPITER study and CPGs, either existing[9 10] or newly developed,[6] to individualize predicted BLR_i and absolute effect of rosuvastatin at 10 years ($ARR_{(target)i}$) among JUPITER's participants. They found an approximate 20-fold variation in the predicted $BLR_{(target)i}$. Thus, the predicted $ARR_{(target)i}$ varied from about 1% to 20% at 10 years, with a slightly different patient stratification depending on the CPG used. Dorresteijn and colleagues then evaluated the application of these individualized predictions to recommend the treatment. They defined the "Number Willing to Treat (NWT)" as the number of patients one is willing to treat in exchange for the prevention of one target outcome event. Its inverse ratio (1/ NWT) was defined as the "decision threshold" and is equivalent to the required $ARR_{(target)i}$ defined for our model. They considered that the treatment receipt per se constituted the harm (fixed harm). Thus, the required $ARR_{(target)i}$ (i.e. 1/ NWT) equaled the $RV_{harm/target(i)}$ (m_2). They examined how the treatment recommendations varied across a range of hypothetical values for the NWT.

2.2. Superiority trial: variable benefit, *variable* harm. Warfarin to prevent cardio-embolic events in patients with atrial fibrillation

Six RCTs compared warfarin versus placebo/no treatment in patients with nonvalvular atrial fibrillation to reduce the occurrence of stroke and systemic cardioembolism. Hart and colleagues meta-analyzed those RCTs and found a pooled RRR for cardio-embolic events (RRR_{stroke}) of 0.64, or 64%, (95% confidence interval [CI] 0.49 to 0.74).[11] On the other hand, warfarin was associated with a pooled RRI for major extracranial bleeding (RRI_{bleed}) of 1.3, or 130%, (95% CI 0.08 to 3.89) (Note: Hart et al. included the intracranial hemorrhages among the strokes in the efficacy analyses[11]).

Several CPGs to predict the risk of stroke and bleeding have been developed and validated in patients with atrial fibrillation. Using the individual predictions for the baseline risk for stroke ($BLR_{stroke(i)}$) and for bleeding ($BLR_{bleed(i)}$), the absolute beneficial effect and also the absolute adverse effect with warfarin can be individualized as,

respectively, $ARR_{stroke(i)} = RRR_{stroke} * BLR_{stroke(i)}$ and $ARI_{bleed(i)} = RRI_{bleed} * BLR_{bleed(i)}$. As an example, for the prediction of the $BLR_{stroke(i)}$, we adopted the $CHADS_2$ score developed on patients off anticoagulation.[12] For the prediction of the $BLR_{bleed(i)}$, we adopted the $HEMORR_2HAGES$ score.[13] Since the $HEMORR_2HAGES$ score was developed on patients on warfarin,[13] the corresponding $BLR_{bleed(i)}$ off warfarin was calculated by dividing the predicted risk on warfarin by 2.3, which is the reported relative risk for major bleeding for warfarin compared to placebo.[11] The results are shown in **Table 3.** The predicted $ARR_{stroke(i)}$ varied from 1.22 to 11.65 %/year and the predicted $ARI_{bleed(i)}$ varied from 0.64 to 4.17 %/year. Comparing the individualized predictions for the benefit and the harm, value-adjusted, we then obtained individualized treatment recommendations for warfarin. A range of plausible values of $RV_{bleed/stroke}$ was examined.

2.2.1. Required $ARR_{stroke(i)}$ to justify warfarin

To justify warfarin, the predicted $ARR_{stroke(i)}$ should be greater than the required $ARR_{stroke(i)}$ (d_1), i.e. greater than $ARI_{bleed(i)} * RV_{bleed/stroke(i)}$ (m_1). Table 3 summarizes the results of the application of the model to individualize warfarin recommendation in a hypothetical patient population, according to the co-classification of patients based on the $CHADS_2$ and $HEMORR_2HAGES$ scores. We arbitrarily chose a group-level relative value for bleed/stroke of 0.6, a relative value calculated from a lost-utility analysis over a 10-year time frame.[4] Table 3 shows the resulting treatment decisions for each of the 42 cells formed according to $CHADS_2$ and $HEMORR_2HAGES$ scores.

As a base case, the table was obtained using for RRR_{stroke} the point estimate (0.64).[11] Since a treatment is accepted as superior compared to placebo/no treatment only when the upper bound of the 95% CI for the relative risk for the target outcome is below 1, we repeated the example using for RRR_{stroke} a value of 0.49 (corresponding to the upper bound for RR_{stroke} 0.51). This corresponds to the worst case, provided that the treatment is beneficial. In that case, the predicted $ARR_{stroke(i)}$ is reduced and fewer patients would be recommended for treatment. For example, a $CHADS_2$ 1 and $HEMORR_2HAGES$ 2 patient would now not be recommended for warfarin treatment (results not shown).

2.2.2. Maximum $ARI_{bleed(i)}$ above which warfarin would not be justified

Figure 2 shows how the maximum $ARI_{bleed(i)}$ (m_3) varies according to different $CHADS_2$ scores and different values of $RV_{bleed/stroke(i)}$ centered on a group-level $RV_{bleed/stroke}$ of 0.6.

2.2.3. Maximum $RV_{bleed/stroke(i)}$ above which warfarin would not be justified

Similarly, given the $CHADS_2$ and the $HEMORR_2HAGES$ scores of the patient, the model can calculate which is the maximum $RV_{bleed/stroke(i)}$ (m_4) such that if the patient assigns a $RV_{bleed/stroke}$ higher than this maximum, warfarin would not be justified. The variation of the maximum $RV_{bleed/stroke(i)}$ according to different $CHADS_2$ and $HEMORR_2HAGES$ scores is depicted in **Figure 3.**

2.3. Individualizing recommendations for a non-inferior treatment

2.3.1. Application of model to non-inferiority trials

The objective of a non-inferiority trial is to show that the effect of a new treatment on a target outcome is not worse, compared to an established effective treatment (EET), by more than a pre-specified margin. This "non-inferiority margin" is the maximum loss of efficacy that is considered acceptable in exchange for a hypothesized *reduction* in harm, value-adjusted. At the design phase, the non-inferiority margin is expressed as either an absolute or relative *increase* in the target event rate. A group-level $RV_{harm/benefit}$ is at least implicit when setting the specified margin. When interpreting the results of a non-inferiority trial at group level, the confidence interval for the observed treatment effect on the target outcome is compared with the non-inferiority margin. If the bound of the confidence interval that reflects the maximal estimate for inferiority is less than the margin (does not "cover" the margin) then it is concluded that the new treatment is non-inferior to EET.

In non-inferiority trials, the CID for a patient can be expressed as the required reduction of the harm which exactly compensates the allowed increase of the target outcome,

value-adjusted. Thus, for application to non-inferiority trials, the equation m_1 can be rewritten as:

required $ARR_{harm(i)} = ARI_{target}/RV_{harm/target(i)}$

2.3.2. Individualization of the results of a trial demonstrating group-level non-inferiority

We individualize group-level results by using CPGs, as applicable (table 2), to predict $BLR_{(i)}$ and thereby absolute treatment effects on the target outcome ($ARI_{target(i)}$) and the treatment harm ($ARR_{harm(i)}$). $ARI_{target(i)}$ is derived as $BLR_{target(i)}*RR_{trial}$. $ARR_{harm(i)}$ is derived as $BLR_{harm(i)}*RRR_{trial}$. We value-adjust the treatment harm for $RV_{harm/target}$. We then compare the individualized predictions of treatment effects on the target outcome and on the harm to derive individualized treatment recommendations. A recommendation to treat with the non-inferior therapy would result when the predicted reduction in harm, value-adjusted, exceeds the predicted loss of efficacy, i.e. when $ARR_{harm(i)}*RV_{harm/target(i)} > ARI_{target(i)}$ (or, holding the same terminology as for superiority trials, when predicted $ARR_{harm(i)}$ > required $ARR_{harm(i)}$).

To examine the worst case, we then repeat the comparison of reduction in harm and loss of efficacy by using for $ARI_{target(i)}$ not the point estimate but the bound of the CI around the point estimate that reflects maximal inferiority of the new treatment.

Discussion

We presented an extension of previously described models to individualize treatment recommendations, based on the use of CPGs to predict individual-level treatment effects, adjusted for the relative importance assigned by the patient to different outcomes.

Strengths. The adoption of an individual-level perspective represents the fundamental feature of the model. The individualizing process requires the conversion of group-level into individual-level treatment effects and the use of the patient's values.[14] The model presented here is more flexible than models for individualizing treatment recommendations previously described.[4 5] Either fixed or variable harm is accommodated in our model. LaHaye and colleagues[15] developed a decision aid specifically designed to individualize antithrombotic therapy in patients with atrial fibrillation that included a variable benefit/variable harm scenario and also the patient's $RV_{bleed/stroke}$. However, they did not explicitly conceptualize and generalize the underlying model. We showed the adaptability of our model to treatments causing multiple kinds of benefits and harms, and to non-inferiority trials. The concepts of the maximum ARI_{harm} and maximum $RV_{harm/benefit}$ that would overturn the clinical decision had not been developed previously. The model is timely, given the increasing number of very large RCTs providing precise group-level estimates of treatment harms as well as treatment benefits, and the recent rapid rise in validated CPGs, catalogued and searchable in *EvidenceUpdates*,[3] that makes the individualization of those group-level quantities more feasible.

Limitations. In our model, we did not include economic costs, either direct or indirect. Like clinical benefits and harms, economic costs can be fixed or variable across patients. This raises the question of whether a group-level cost-effectiveness analysis of a treatment can be individualized.[16] A step in that direction is to apply prognostic models to particularize group-level information on cost-effectiveness according to predicted risk and patient sub-group.[17] Our model provides a method for individualizing

the consequences of treatment. However, analyses of incremental cost-effectiveness or cost-utility at the individual level are constrained at present by lack of reliable individualized data on the incremental direct and indirect costs of treatment.

Use and appropriateness of CPGs for individualizing recommendations. We generically explained why, how and when the model building requires the use of CPGs. CPGs are developed for different purposes. A particular application of a CPG is to individualize risk predictions in the control group of an RCT. There are some desirable features of a CPG for this specific application. In the **box** we provide an aid to guide the user in the search for and the evaluation of an appropriate CPG for individualizing the group-level results of the RCT of interest.

In the case of variable benefit/variable harm, we look for two different CPGs to classify the patients according to the "baseline" risks for the target event and for the harm. In this case the predictions resulting from this co-classification might be constrained by a possible within-patient correlation between the two variable risks, since the target event and the harm may share some risk factors or may not be independent outcomes.

Uncertainty in group-level estimates and patient values. The results of an RCT are usually provided as point estimates accompanied by a measure of variability (confidence interval). Often the within-trial estimates for the harm have been characterized by high imprecision. However this situation may be improving with the increasing reports of very large active-control RCTs.[18]

Probably the major source of uncertainty is the patient's $RV_{harm/benefit}$ and its elicitation. The scenario presented to the patient uniformly should include the major clinical outcomes of the treatment decision, including death if relevant, and the time frame of the consequences of the decision. Decision aids, tools specifically designed to prepare the patient to participate in the decision process, have been shown to improve patient knowledge and involvement, especially when they target explicit values clarification.[19]

One may embed in the calculation of the individual quantities a measure of the variance (e.g. standard error) of the group-level measures entering the model.[20] Additionally, one may estimate how much that uncertainty can affect the individual predictions in the most pessimistic direction, i.e. using the CI bounds for the group-level estimate of the treatment effect on target corresponding to the worst scenario. We proposed an alternative approach to deal with the uncertainty around the quantities entering the model. We provided formulas for estimating the individualized maximum ARI_{harm} and $RV_{harm/benefit}$ above which the decision to treat would be overturned.

Future research objectives.

a) Net benefit and model validation. Vickers and colleagues[5] conceived a method to empirically test whether individualized recommendations based on CPG-based predictions of absolute treatment effects, value-adjusted, would actually result in real life in a greater *net benefit* compared to a policy of treat all patients, or compared to treat none. The method utilizes the distribution of predicted individualized treatment effects in the randomly allocated treatment and control groups of a large RCT. One combines the patients whose predicted $ARR_{target(i)}$ exceeded the required $ARR_{target(i)}$ who were randomized to the treatment group, and the patients whose predicted $ARR_{target(i)}$ did not exceed their required $ARR_{target(i)}$ who were randomized to the control group. Those are the patients, respectively, who would or would not be recommended for treatment, were prediction-based treatment used in real life. One then compares the observed outcomes in the trial of that combined group with the outcomes for the treatment arm of the RCT. The superiority of the prediction-based policy is validated if its net benefit is greater than the net benefit of treat all, or treat none. The empirical result, in the examples of Vickers et al.,[5] and later Dorresteijn,[6] was that a prediction-based policy was superior over a limited range of required $ARR_{target(i)}$. If the required $ARR_{target(i)}$ was extreme in either the low or high direction, a policy of treat all or treat none, respectively, was preferred.

Vickers[5] and Dorresteijn[6] used this approach to validate individualized recommendations in a fixed harm scenario, where the harm was receipt of the

treatment per se. Nevertheless, the same approach can be used to validate individualized recommendations in variable harm scenarios, and for treatments tested in non-inferiority as well as superiority trials. As with Vickers' method in general, individual-patient trial data must be available to identify the patients whose predicted $ARR_{target(i)}$ did or did not exceed their required $ARR_{target(i)}$.

Contributors: Dr Marcucci designed and carried out the data analyses, interpreted the results, drafted and revised the manuscript. Dr Sinclair designed and carried out the data analyses, interpreted the results, drafted and revised the manuscript. Each author had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgement: We thank Dr Brian Haynes, Nancy Wilczynski and Dr Alfonso Iorio at the Health Information Research Unit, McMaster University Health Sciences, for stimulating discussions and support.

Competing interest: Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that MM and JCS do not have support from and have no relationships with any company that might have an interest in the submitted work in the previous 3 years; MM and JCS have no non-financial interests that may be relevant to the submitted work.

Funding: MM: none. JCS: none

Data sharing: no additional data available.

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Table 1

Quantities required for generalized model for individualizing treatment recommendations

Element	Group-level measures		Individualized predictions	
	Quantity	Measured as	Quantity	Predicted as
Benefits	RRR_{trial}	$1\text{-}RR_{trial}$ or $1\text{-}HR_{trial}$	ARR_i	$RRR_{trial} * BLR_i$ for benefit[1]
Harms				
fixed	ARI_{trial}	$Risk_{treated-control}$	ARI_i	ARI_{trial} used as ARI_i
variable	RRI_{trial}	$RR_{trial} - 1$ or $HR_{trial} - 1$		$RRI_{trial} * BLR_i$ for harm[2]
Values	RV	$V_{harm}/V_{benefit}$	RV_i	Provide a range of RVs centered on typical group-level RV[3]

[1] Estimate BLR_i for benefit using CPG for individualized prediction of outcome comprising the benefit

[2] Estimate BLR_i for a variable harm using CPG for individualized prediction of outcome comprising the harm

[3] Estimate typical RV from formal utility-based analyses, patient groups, or expert opinion

RRR_{trial}: relative risk reduction observed in RCT(s). ARI_{trial}: absolute risk increase for a fixed harm. RRI_{trial}: relative risk increase for a variable harm, from RCT(s) or best evidence. RR: relative risk. HR: hazard ratio. RV: relative value. BLR: baseline risk (risk in control group). ARR_i, ARI_i, BLR_i, RV_i: individualized predicted estimates. CPG: clinical prediction guide

Table 2. Clinical Prediction Guides for individualizing treatment effects

Type of Trial	Type of Control	CPG to predict control risk for *target event*: population	CPG to predict control risk for *harm*: population
Superiority trial	Placebo or no treatment	CPG developed on patients on placebo or no treatment	Fixed harm: CPG not needed
			Variable harm: CPG developed on patients on placebo or no treatment**
	Active control (EET)	CPG developed on patients on EET*	Fixed harm: CPG not needed
			Variable harm: CPG developed on patients on EET
Non-inferiority trial	Active control (EET)	CPG developed on patients on EET*	Fixed harm: CPG not needed
			Variable harm: CPG developed on patients on EET

CPG, Clinical Prediction Guide; EET, Established Effective Therapy

*If a validated CPG developed on patients on placebo or no treatment is used, the individualized risk for the target event while on EET can be obtained by multiplying the risk off treatment by the group-level relative risk for the target event on EET compared to placebo or no treatment

** If a validated CPG developed on treated patients is used (*see worked example on warfarin*), the individualized risk for the harm off treatment can be obtained by dividing the risk on treatment by the group-level relative risk for the harm with the treatment compared to placebo or no treatment

Table 3. Application of prognostic risk scores for variable treatment benefit, variable treatment harm to particularize a treatment recommendation. Theoretical example: Warfarin for stroke reduction in patients with atrial fibrillation

					Risk for stroke ($CHADS_2$)						
				Score	0	1	2	3	4	5	6
Risk for bleed ($HEMORR_2HAGES$)				Predicted BLR_{stroke}, %/yr	1.9	2.8	4.0	5.9	8.5	12.5	18.2
	Predicted BLR_{bleed}, %/yr warfarin			**Predicted ARR_{stroke}, %/yr***	**1.22**	**1.79**	**2.56**	**3.78**	**5.44**	**8.00**	**11.65**
Score	yes	no	Predicted ARI_{bleed}, %/yr**	**Required ARR_{stroke} @ $RV_{bleed/stroke}$ 0.6**	***Treatment recommendation***						
0	1.9	0.83	1.07	**0.64**	**T**	**T**	**T**	**T**	**T**	**T**	**T**
1	2.5	1.09	1.41	**0.85**	**T**	**T**	**T**	**T**	**T**	**T**	**T**
2	5.3	2.30	3.00	**1.80**	**DT**	**CC**	**T**	**T**	**T**	**T**	**T**
3	8.4	3.65	4.75	**2.85**	**DT**	**DT**	**DT**	**T**	**T**	**T**	**T**
4	10.4	4.52	5.88	**3.53**	**DT**	**DT**	**DT**	**T**	**T**	**T**	**T**
≥ 5	12.3	5.35	6.95	**4.17**	**DT**	**DT**	**DT**	**DT**	**T**	**T**	**T**

BLR: baseline risk. ARR : absolute risk reduction. ARI: absolute risk increase. RV: relative value. T: Treat. **DT**: Don't treat. **CC**: Close call
* Predicted ARR_{stroke} if RRR_{stroke} is 0.64 (RR 0.36) using warfarin[11]. ** Predicted ARI_{bleed} if RRI_{bleed} is 1.30 (RR 2.30) using warfarin[11].

Legends for Figures

Figure 1

Title: Models for individualizing treatment

Variable benefit/fixed harm (Panel A) and variable benefit/variable harm (Panel B) models are shown. In each model, treatment benefit, modeled as absolute risk reduction for the target event, varies directly with baseline risk for the target event. Treatment harm is modeled as the absolute risk increase for the harm of treatment. Harm is then value-adjusted based on a relative value (RV) assigned to the treatment harm as compared to the target event prevented. With a fixed harm (Panel A), the absolute risk increase for the harm of treatment is constant. With a variable harm (Panel B), the absolute risk increase for the harm of treatment varies with the baseline risk for the harm. As indicated by the arrow in each panel, the point at which the value-adjusted treatment harm intersects the treatment benefit defines the clinically important difference (CID) for the treatment benefit.

Figure 2

Title: Maximum ARI_{bleed} for treatment to be justified, by $CHADS_2$ score and relative $value_{stroke/bleed}$

The scatter plot shows the maximum ARI_{bleed} (%/yr) above which warfarin would not be justified, according to the $CHADS_2$ score and different $RV_{bleed/stroke}$. The horizontal lines depict the predicted ARI_{bleed} with warfarin for each $HEMORR_2HAGES$ score. As examples: at $RV_{bleed/stroke}$ 0.6, we would treat $CHADS_2$ score 0 patients only if their predicted ARI_{bleed} given warfarin were less than 2.0%/yr. Accordingly, we would treat $HEMORR_2HAGES$ score 0 - 1 patients because their predicted ARI_{bleed} (1.1, 1.4 %/yr [table 2]) is less than 2.0%/yr. We would not treat $HEMORR_2HAGES$ score ≥ 2 patients because their predicted

ARI_{bleed} (3.0 – 7.0 %/yr [table 2]) is greater than 2.0%/yr. Again at $RV_{bleed/stroke}$ 0.6, we would treat $CHADS_2$ score 2 patients only if their predicted ARI_{bleed} were less than 4.3%/yr. Thus, we would treat $HEMORR_2HAGES$ score 0 – 2 patients because their predicted ARI_{bleed} (1.1 – 3.0 %/yr [table 2]) is less than 4.3 %/yr. We would not treat $HEMORR_2HAGES \geq 3$ patients because their predicted ARI_{bleed} (4.8 – 7.0 %/yr [table 2]) is greater than 4.3 %/yr. At $RV_{bleed/stroke}$ set higher or lower than 0.6, fewer patients or more patients, respectively, would be recommended for treatment according to the model.

Figure 3

Title: Maximum relative $value_{bleed/stroke}$ for treatment to be justified, by $CHADS_2$ score and $HEMORR_2HAGES$ score

The scatter plot shows the variation of the maximum $RV_{bleed/stroke}$ according $CHADS_2$ and $HEMORR_2HAGES$ (abbreviated as HEMO) scores. The horizontal lines depict 3 illustrative maximum relative values. The model predicts the maximum $RV_{bleed/stroke}$ to vary over a range between 0.1 (i.e. a value assigned to a stroke 10 times higher that that assigned to a major bleeding) and about 10 (i.e. a value assigned to a major bleeding 10 times higher that that assigned to a stroke). As examples, the insert zooms in the results for patients with $CHADS_2$ score of 0-2 and HEMO score of 0, 2 and 4. Among patients with $CHADS_2$ score of 0, warfarin would be recommended for HEMO 0 patients if their $RV_{bleed/stroke}$ were <1.1; for HEMO 2 patients, if their $RV_{bleed/stroke}$ were <0.4; for HEMO 4 patients if their $RV_{bleed/stroke}$ were <0.2. For patients with $CHADS_2$ score of 2, warfarin would be recommended for HEMO 0 patients if their $RV_{bleed/stroke}$ were <2.3; for HEMO 2 patients if their $RV_{bleed/stroke}$ were <0.8; for HEMO 4 patients if their $RV_{bleed/stroke}$ were <0.4.

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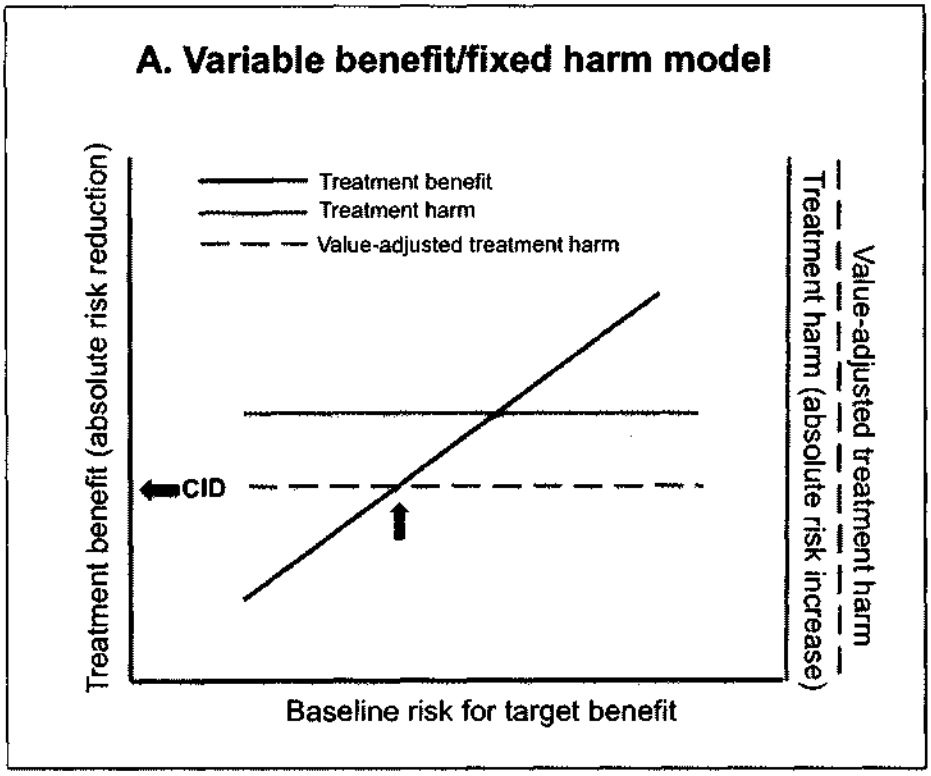
Figure 1. Models for individualizing treatment



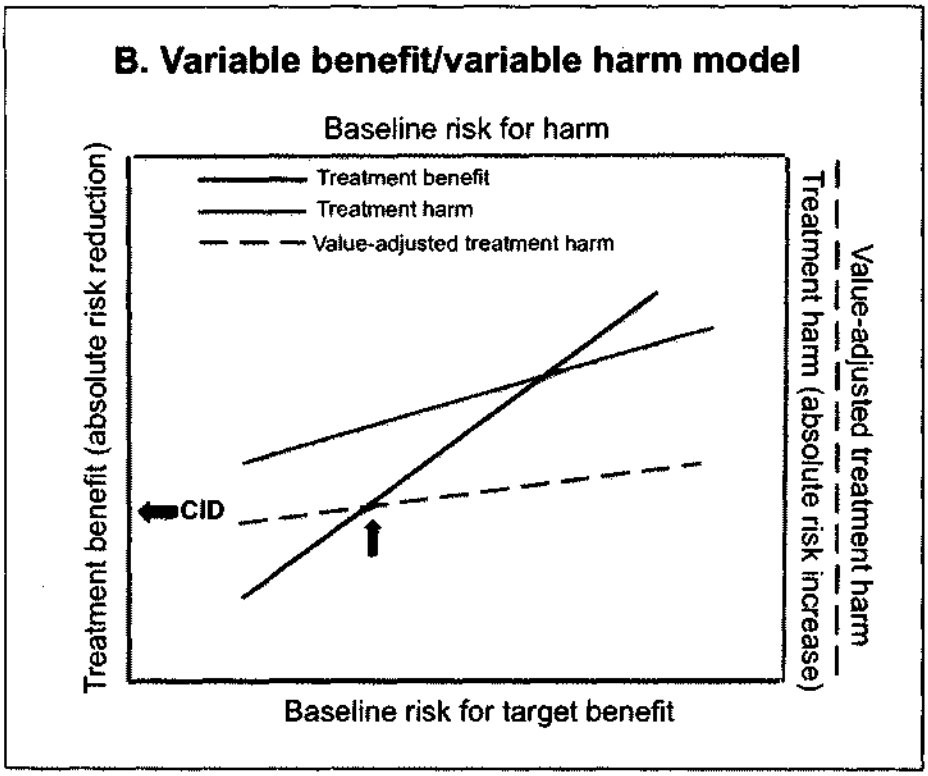
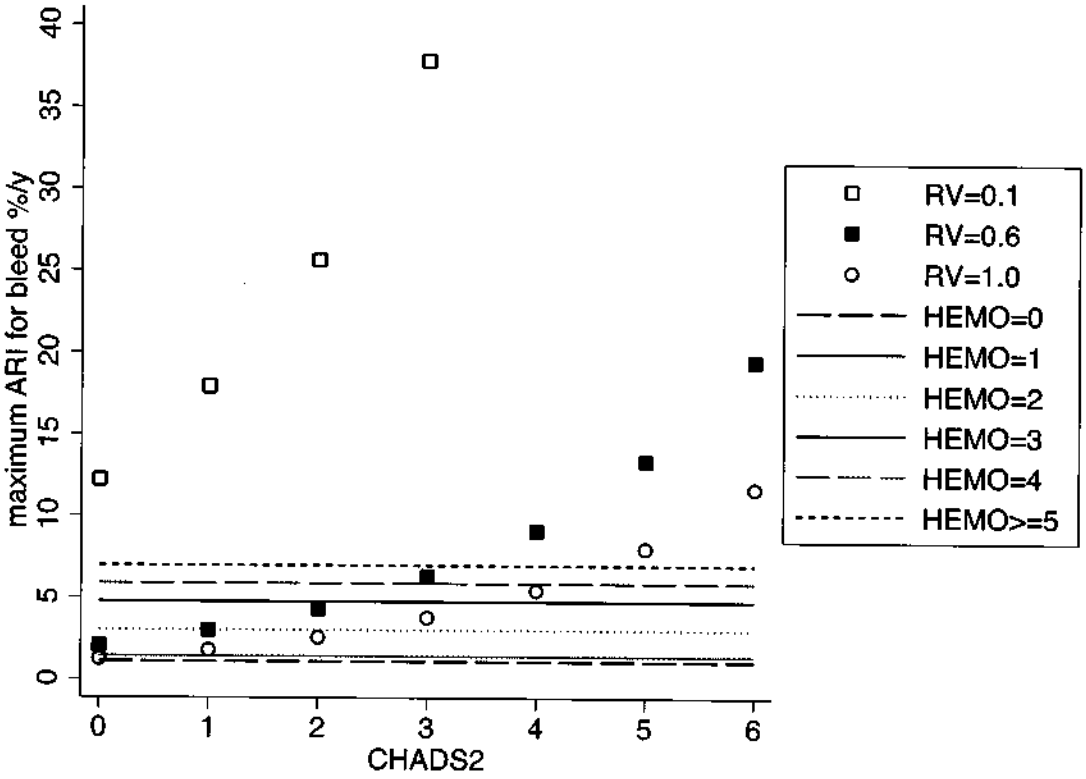
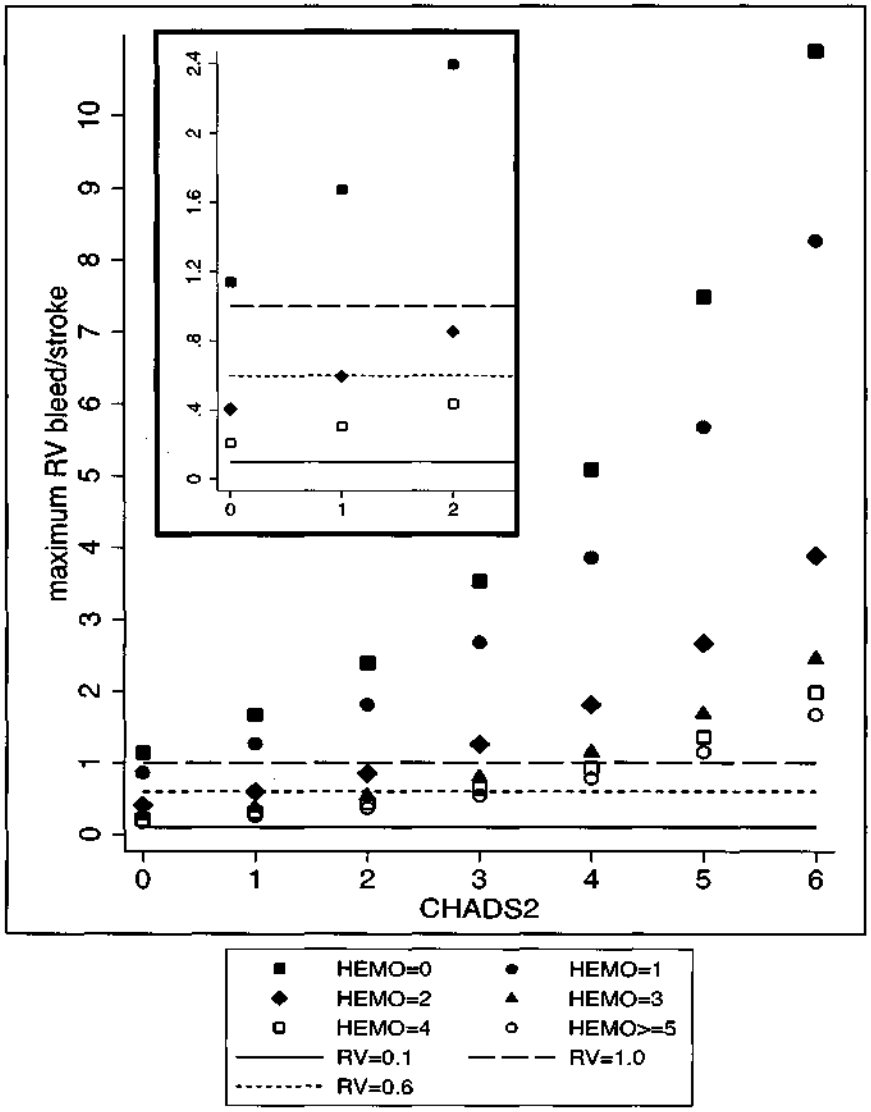


Figure 2. Maximum ARI_{bleed} (%/yr) for warfarin to be justified, by $CHADS_2$ score and $HEMORR_2HAGES$ scores



05791

Figure 3. Maximum $RV_{bleed/stroke}$ for warfarin to be justified, by $CHADS_2$ and $HEMORR_2HAGES$ scores



Box. How to use a CPG on risk prediction to individualize the results of an RCT

Relevance

Will the CPG help me in making individualized risk predictions for patients in the control group of the RCT of interest?

- Were the patients on whom the CPG was developed or validated similar to the RCT's control group as regards their clinical characteristics?
- Does the treatment status of the patients on whom the CPG was developed match that of the RCT's control group, i.e. each on no treatment or placebo; each on established effective therapy?
- Does the CPG provide the absolute risk (or is it at least derivable) for the outcome of interest (target event or harm), in a specified period of time, according to risk factors/risk score?

Validity

Are the predictions made by the CPG valid?

- How was the CPG developed?
    - Was the CPG developed on a well-defined and representative sample of patients prospectively followed up?
- How well did the CPG perform in the population of derivation?
    - Was the CPG's calibration tested? How accurate were the predictions of the absolute risk, i.e. how good was the agreement between predictions and observed outcome?
    - Were the CPG's discrimination (c-statistic) and reclassification tested? How good were they?
    - Did the CPG undergo internal validation to quantify and eventually adjust for overfitting/optimism?
- Did the CPG undergo external validation?
    - Was the CPG's performance tested in patients different from those on whom it was developed? How good was it?

Precision

How precise were the predictions of the absolute risk, i.e. how wide was the uncertainty around the provided estimates?

Appendix: Algebraic derivation of the models

Legend:

Target = target outcome that the treatment can prevent

Harm = any increase of an adverse outcome due to the treatment

CID = clinically important difference

ARR = absolute risk reduction

ARI = absolute risk increase

V = value

RV = relative value

1. Derivation of the simple model (one benefit, one harm)

The CID corresponds to the ARR for the target benefit sufficiently large to exactly offset the treatment harm. Allowing for a different value assigned to the target outcome prevented by the treatment and to the harm caused by the treatment (V_{target} and V_{harm}, respectively), the condition at the CID can be expressed algebraically as:

$$\mathbf{ARR_{target} * V_{target} = ARI_{harm} * V_{harm}} \qquad \mathbf{(1)}$$

1.1. Algebraic solution for the required $ARR_{benefit}$ to offset the treatment harm

Dividing each side of the equation (1) by V_{target}

$ARR_{target} = ARI_{harm} * V_{harm}/V_{target} \rightarrow$

$$\textit{required } \mathbf{ARR_{target} = ARI_{harm} * RV_{harm/target}} \qquad \mathbf{(2)}$$

1.2. Algebraic solution for the maximum ARI_{harm} above which treatment would not be justified

Dividing each side of the equation (1) by V_{harm}

$ARR_{target} * V_{target} / V_{harm} = ARI_{harm} \rightarrow$

$ARR_{target} * RV_{target/harm} = ARI_{harm} \rightarrow$

maximum $ARI_{harm} = ARR_{target} * RV_{target/harm}$

or, expressed in terms of $RV_{harm/target}$

maximum $\mathbf{ARI_{harm} = ARR_{target} / RV_{harm/target}}$ **(3)**

1.3. Algebraic solution for the maximum $RV_{harm/target}$ above which treatment would not be justified

$ARR_{target} = ARI_{harm} * V_{harm} / V_{target} \rightarrow$

$ARR_{target} = ARI_{harm} * RV_{harm/target}$

dividing each side of equation by ARI_{harm}

$ARR_{target} / ARI_{harm} = RV_{harm/target} \rightarrow$

maximum $\mathbf{RV_{harm/target} = ARR_{target} / ARI_{harm}}$ **(4)**

2. Derivation of the complex model (multiple benefits, multiple harms)

Legend:

Benefit = any reduction of an adverse outcome additional to the target outcome

At the CID, the sum of treatment benefits offsets the sum of treatment harms. Allowing for different values for every outcome prevented or caused by treatment, this can be expressed algebraically as:

$$ARR_{target}*V_{target} + ARR_{benefit(2)}*V_{benefit(2)} +...+ ARR_{benefit(m)}*V_{benefit(m)} = ARI_{harm(1)}*V_{harm(1)}+ ...+ ARI_{harm(k)} * V_{harm(k)} \quad (5)$$

where m is the total number of treatment benefits, the benefit(2) to benefit(m) are the benefits other than the target one, and k is the number of treatment harms. Or, likewise:

$$ARR_{target}*V_{target} + \sum_{(for\ j=2\ to\ m)} ARR_{benefit(j)}*V_{benefit(j)} = \sum_{(for\ j=1\ to\ k)} ARI_{harm(j)}*V_{harm(j)} \quad (6)$$

Subtracting $\sum_{(for\ j=1\ to\ m)} ARR_{benefit(j)}*V_{benefit(j)}$ from both sides and dividing both sides for V_{target}, we can obtain the required ARR_{target} such that the total treatment benefits offset the total treatment harms:

$$\text{required } ARR_{target} = \sum_{(for\ j=1\ to\ k)} ARI_{harm(j)}*RV_{harm(j)/target} - \sum_{(for\ j=2\ to\ m)} ARR_{benefit(j)}*RV_{benefit(j)/target} \quad (7)$$

where every RV is expressed as the value of that outcome, prevented or caused by the treatment, compared with the value assigned to the target outcome.

05796
05796

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Subject: Re: the replacements.....
Date: Monday, April 29, 2013 8:22:04 PM

Would the SACHRP need to be vetted for conflicts as well as expertise?

As far as a potential response --
I would go back to Sally Howard's question - did the science at the time of. The research establish a foreseeable risk of increased mortality for the subjects receiving oxygen levels at the lower end of the standard of care?

And did the protocol demonstrate that the researchers believed there was an increased risk of mortality?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, April 29, 2013 08:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: the replacements.....

Okay.

Thanks

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, April 29, 2013 8:12 PM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: the replacements.....

No
Only the addressee- it is in the italicized portion of the March 7 letter
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, April 29, 2013 08:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: the replacements.....

Was anything else substantively changed in the letter?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, April 29, 2013 8:08 PM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: the replacements.....

The original letter was also addressed to the IRB folks at RTI (the DCC for the NRN). Apparently, RTI contacted OHRP, told them they were a DCC and didn't enroll patients so the letter was changed. RTI then became a CC instead of an addressee.

Thanks for your help- let me know if I can provide anything else

Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, April 29, 2013 07:47 PM
To: Devaney, Stephanie (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: the replacements.....

Steph/rose,
The OHRP letter at
http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf says at the top that it replaced the letter sent a month earlier. Can you remind me what the key differences are between the feb and march letters?

Nice thing is that it provides a precedent to replace the letter one more time!!

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"
Subject: RE: SUPPORT call
Date: Monday, April 29, 2013 3:50:00 PM

They don't want to do it!!

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, April 29, 2013 3:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT call

I don't think Jon is changing his mind or changing anybody else's! Perhaps we just have a subcommittee vote?

Abhik Das, Ph.D.
Senior Research Statistician
RTI International
6110 Executive Blvd., Suite 902
Rockville, MD 20852-3903
e-mail: adas@rti.org
Phone: 301-770-8214
Fax: 301-230-4646

From: Das, Abhik
To: Bell, Edward (Pediatrics); Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: DUA forms
Date: Monday, April 29, 2013 3:42:31 PM

To share forms with external NRN investigators we normally need SC approval. If RTI releases any data, we need a DUA (specific to the proposal). If center investigators review existing GDB/FU data (edited/cleaned data that we supply annually) for any reason (not just forms), we need to have them sign the GDB/FU Grantee agreement. Non-NRN collaborators, if reviewing existing aggregated NRN data, can sign the Grantee agreement if at Iowa.

Rose can correct me if my understanding is incorrect.

Thanks

Abhik

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Monday, April 29, 2013 3:14 PM
To: Das, Abhik; Rosemary Higgins
Subject: RE: DUA forms

Rose,
I've always had potential collaborators sign the DUA that all our investigators sign each year (attached). It seems like they should sign something if we are going to share data forms with them (but not data). If the DUA only applies to actual data, then we shouldn't need to have all our staff sign this every year. What am I missing? Do we need a vote to allow two investigators at a non-NRN site to see the SUPPORT data forms to help write a proposal for a secondary analysis? And what about an Iowa pediatric anesthesiologist who is advising Frank Morriss on his proposal for a prospective time-limited study of anesthesia and surgery exposure and their impact on NDI in very preterm infants?
Ed

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, April 29, 2013 2:06 PM
To: Bell, Edward (Pediatrics)
Cc: Rosemary Higgins
Subject: RE: DUA forms

I think this form is for sharing actual data. For just sharing the forms, I am not sure we have a form for that purpose. Maybe that needs a steering committee or subcommittee vote?

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Monday, April 29, 2013 2:59 PM
To: Das, Abhik
Cc: Rosemary Higgins
Subject: FW: DUA forms

Abhik,

I would like to share the SUPPORT data forms with two potential collaborators from a non-NRN site for the purpose of developing a proposal for a new analysis using SUPPORT data. Is the attached form appropriate to have them sign, or is there something better?
Thanks,
Ed

From: Bell, Edward (Pediatrics)
Sent: Monday, April 29, 2013 1:33 PM
To: Kristin Zaterka-Baxter; Meg Cunningham
Subject: RE: DUA forms

Is this also the form we use for collaborators from non-NRN sites?

From: Bell, Edward (Pediatrics)
Sent: Monday, April 29, 2013 12:52 PM
To: Kristin Zaterka-Baxter; Meg Cunningham
Cc: Morriss, Frank
Subject: DUA forms

Kris or Meg,
We are recruiting an Iowa anesthesiologist as an unpaid consultant and perhaps future collaborator for Frank Morriss's prospective time-limited collection of data on surgery and anesthesia exposure for GDB babies. Is the attached form the best one to have him sign, or is there a more appropriate form? I assume we can just have him add his signature at the end of the attached form.
Thanks,
Ed

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]
Subject: Re: quick question
Date: Monday, April 29, 2013 2:52:41 PM
Attachments: image001.png

Yes, correct
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Monday, April 29, 2013 02:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: quick question

Thank you! I have it (from you actually) ☺ It's dated March 22nd right?

I'll let Kathy know that it's not public. Thank you!

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, April 29, 2013 2:49 PM
To: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: quick question

No
The letter to UAB is the March 7 determination letter from OHRP to UAB. The UAB response is not public – would you like it? They shared it with me.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Monday, April 29, 2013 2:48 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: quick question

Hi Rose –

See Kathy's email below (I just sent her these things – she's off-site). Is the UAB response to OHRP public?

Steph

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, April 29, 2013 2:36 PM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: can you send

Link to uab protocol, the template consent as attachment, and link to ohrp letter to uab (is uab response public?)

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

From: Finer, Neil
To: rose higgins; Wally Carlo
Subject: FW: Federal Coordinating Council on Comparative Effectiveness Research to Hold Public Listening Session in Chicago on May 13
Date: Monday, April 29, 2013 1:35:15 PM

Hi Rose
I do not know if you or other members of the NRN are planning to attend
this session and make a presentation
I would think it would be a great idea
Neil
Here is the link

>http://www.hhs.gov/news/press/2009pres/05/20090507c.html

From: Bell, Edward (Pediatrics)
To: Das, Abhik; Shankaran, Seetha; Barbara Stoll; Wally Carlo, M.D.; Walsh, Michele; Krisa Van Meurs; Abbot Laptook; Brenda B Poindexter; Fanaroff, Avroy; Ivan Frantz; Goldberg, Ron; Kathleen Kennedy; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; Kurt Schibler; Pablo Sanchez; Richard A. Ehrenkranz <; paul costello; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Paul Costello
Subject: More SUPPORT
Date: Monday, April 29, 2013 12:27:34 PM
Attachments: Lantos - Chron Higher Educ 2013.pdf

Here is another commentary by John Lantos:
http://chronicle.com/blogs/conversation/2013/04/19/preemies-need-protection-but-not-the-kind-you-think/.

THE CHRONICLE
of Higher Education

Preemies Need Protection, but Not the Kind You Think

April 19, 2013, 12:35 pm
By John D. Lantos

The controversy over a recent neonatal clinical trial of oxygen therapy for premature babies offers two starkly different prescriptions for protecting babies from risky treatments in neonatal intensive care units.

One view, advocated by the federal Office for Human Research Protections and the advocacy group Public Citizen, is to warn their parents that participating in important, well-designed clinical trials is risky. Public Citizen even suggests prohibiting such studies altogether. The OHRP views the trial as one that involved "substantial risks," because "the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death." Public Citizen viewed the study as "highly unethical" because it "exposed 1,316 extremely premature infants to increased risks of either death or retinal damage." The advocacy group called upon Health and Human Services to apologize to the parents of the babies who were enrolled in this study.

The researchers, the institutional review boards, and the Eunice Kennedy Shriver National Institute of Child Health and Development, which sponsored the study, apparently disagreed. In designing, reviewing, and conducting the study, they feared that the biggest risk to premature babies was to be treated with potentially toxic doses of oxygen while their doctors did not know which doses were safest. Instead of continuing these potentially risky practices, they decided to study the safety and effectiveness of different levels of oxygen. They didn't think that the study added any risk to conventional therapy and so did not warn parents of potential risks.

At the outset of the study, reasonable people disagreed about the best dose of oxygen. Some thought that lower doses of oxygen were safer, others thought the higher doses were safer. Before the study was done, babies throughout the United States would get any and all doses within the range of acceptable doses, based upon the untested and therefore unscientific beliefs of their physicians. The study was designed to protect babies from the risks of these unscientific and necessarily idiosyncratic treatment choices.

So who is right? Was the study riskier than conventional treatment? If so, parents should clearly have been warned of these risks. If not, then no such warning was necessary.

Luckily, for this particular study, we know the answer. That is because the institutions involved collected and published data on all premature babies, not just those in the study. They can be found in two papers, one in *The New England Journal of Medicine* and one in *Pediatrics*. The first, published May 2010, reported survival rates and rates of severe eye disease for all outcomes for babies in the randomized trial. The other, published August 23, 2010, reported the same outcomes for all babies in the neonatal research network.

Here is what the data show. The babies in the "low oxygen" arm of the clinical trial had a mortality rate of 19.9 percent. The babies in the "high oxygen" arm of the study had a mortality rate of 16.2 percent. Babies in the network over all had a mortality rate of 24 percent. For severe retinopathy, the numbers are 8.6 percent (low oxygen group), 17.9 percent (high oxygen group) and 24.1 percent (overall group). These data have been available for three years. It is inexplicable that neither OHRP nor Public Citizen seem to be aware of these data or, if they are, that they can still claim that babies in the study were harmed by being denied conventional therapy.

When the study was designed, there was no reason to believe that being in the study and thus being randomized to higher or lower levels of oxygen was riskier than the standard treatment at the time. The data confirmed this prediction. Far from exposing babies to risk, the

studies protected babies from the risks of conventional therapy. The study not only protected the babies in the study. It will protect hundreds of thousands of babies in the future from similar uncontrolled therapy.

It is shocking that OHRP and Public Citizen did not see fit to understand the study or to read the results before claiming that it was risky to babies. The study protected babies. Reckless and ill-informed opinion about highly ethical scientific studies is what truly puts babies at risk. It is OHRP and Public Citizen, not the investigators, who should apologize for irresponsible regulatory overreach and for egregious misinterpretations of the goals, conduct, risks, and results of an important study. Babies need to be protected from advocates like these.

John D. Lantos is professor of pediatrics and director of the Pediatric Bioethics Center at Children's Mercy Hospital in Kansas City, Mo. He is the author (with William Meadow) of Neonatal Bioethics: The Moral Challenges of Medical Innovation *(Johns Hopkins University Press, 2005). He was not involved in the oxygen-therapy trial in any way. Children's Mercy Hospital is now a part of the NICHD Neonatal Research Network but was not at the time of the study in question.*

(Photo from Flickr/Creative Commons)

This entry was posted in Medicine. Bookmark the permalink.

rpm13 1 week ago

This is a false argument. The issue is why wouldn't the researchers do what almost all researchers are required to do, even those doing near-zero risk studies: obtain informed consent (from parents)? Beneficence is only one principle of ethical research. Justice and respect for persons are equally important.

Trey Medley 6 days ago in reply to rpm13

The issue, as I understand it, is that there was no increase in risk. There has previously been not only no regulation, but no guidelines for the amount of oxygen to use (within certain parameters) s therapy from premature babies. The study simply worked within the already established parameters to discern which end (high or low) was better. Since there has previously been no guidelines, there was no control group against which to evaluate "risk". Thus it could not have been a case of any increased risk. The risk present was the risk inherent in the situation: a premature baby. The baby would have received oxygen therapy regardless, and it would have been either high, low, or fluctuating. The study merely eliminated the fluctuation and opted to track which infants received only high and which received only low (er) levels of oxygen therapy. Since this was not a new practice (or initiating a level of oxygen therapy), there was no new form of therapy being investigated. Since that is the case the presumed risk could not be higher. Given that the actual mortality was lower than in untracked therapies, the actual risk was lower. In any way that the study is analyzed it was either safer (using results) or as safe (not taking into account results) as the standard therapy (in fact it "was" the standard therapy). Thus no informed consent was required because the therapy was already established practice. It was not a study in the traditional sense, but merely a tracking of the results of a study. Nothing new or experimental (in the sense of untried) was being used. It was not "near-zero" it was "zero" or "negative" risk.

rpm13 6 days ago in reply to Trey Medley

If this was a retrospective study in which reseachers merely tracked outcomes for babies whose clinicians assigned oxygen levels according to there own best clinical judgment, you are right that there was no increased risk to inform parents about. But if it is a randomized trial, oxygen level is determined by chance and the parents had a right to know that the level assigned to their infant might have consequences that could not be known until the study was completed. You can't claim that it was a foregone conclusion that there would be no consequences and still claim that the study could yield valuable information. I do not know for sure which kind of study this was. If you think of informed consent as a process to make subjects understand the study in which they are enrolling, rather than a legal document, it's very possible to get parents to understand the consequences of random assignment within a range of standard practice. So my question remains: why not do that? The answer could be telling.

1 person liked this. Like

Dr. Jillian T. Weiss 1 week ago

The claim wasn't that any particular oxygen therapy was risky; it is clear that they all have elements of risk. The issue here is informed consent - were the patient's parents informed of the risks before they signed on? Provision of medical services without informing the patient of the risk, which services thereby result in injury falling within the risk zone, is medical negligence.

10 people liked this. Like

jkattwinkel 1 week ago in reply to Dr. Jillian T. Weiss

The parents did sign consent forms to enroll in the study. The criticism was that the consent may not have been sufficiently specific about the risks of slightly higher vs slightly lower concentrations of oxygen.

The critique cited historical studies showing very high concentrations to be associated with eye damage and very low concentrations associated with cerbral palsy and higher mortality - all such studies conducted long before there was the technology for measuring oxygen reaching the tissues. So these earlier studies involved inspired oxygen concentrations either far greater or far below those used in the current study. In the post-oximetry era (past 5-10 years), the standard of care has been to administer sufficient oxygen to keep blood oxygen in the 85-95% oxyhemoglobin saturation range - some advocating the higher end, others the lower end. There was no evidence that using either strategy would result in more risk.

Type your comment here

Criticizing the investigators for not warning the parents of the unexpected findings of a study yet to be done is Monday morning quaterbacking. This was a valuable study with an unanticipated outcome that will will improve the quality of care. Furthermore, it appears that the babies benefited from the study via a "Hawthorne effect" (i.e., studying an issue improves performance).

10 people liked this. Like

Peter Hess 1 week ago in reply to jkattwinkel

This is an important clarification. The omission of it in the original piece seems careless. My first reaction (as a layperson) was the same as Dr. Weiss's.

Even with the new information provided by jkattwinkel, the insistence on "sufficiently specific" information in the informed consent consultation and documentation seems valid - and well within the purview of patient advocacy groups -- *especially* given the statistics cited in the article (which Dr. Weiss recaps).

Though both sides seem, from this discussion, to have made errors in judgement, which (if such is the case) certainly deserve mention, the calls for a public apology by either group smacks of 24 hour news-cycle grandstanding, and doesn't advance anything.

2 people liked this. Like

EllenHunt 6 days ago in reply to Peter Hess

Those statistics CAME FROM the study! Thimk.

So what would be the point of more verbiage? Let's say you were a parent and you were told, "enrollment in this study might be harmful to your child's vision or survival".
Ok. And? Reality is that not being enrolled in the study could be harmful to your child's vision or survival. Nobody knew the results beforehand. Preemies die all the time.

Like

fisherman1 1 week ago

The discussion of eye damage(retina) vs brain damage was apparently shallow. The retrolentro-prematurity has been shown to be more complex since first observed in the very late thirties and early forties. Genetics has recently been suggested as a cause among a few other possibilities.

2 people liked this. Like

old nassau'67 6 days ago

The babies in the "low oxygen" arm of the clinical trial had a mortality rate of 19.9 percent. The babies in the "high oxygen" arm of the study had a mortality rate of 16.2 percent. Babies in the network over all had a mortality rate of 24 percent. For severe retinopathy, the numbers are 8.6 percent (low oxygen group), 17.9 percent (high oxygen group) and 24.1 percent (overall group).

The numbers pose a Scylla - Charybdian problem: high oxygen has the lowest mortality of the three groups, but twice the severe retinopathy of the low oxygen group.
What's the poor doctor to do?

2 people liked this. Like

EllenHunt 6 days ago in reply to old nassau'67

Save the child. You are presuming that retinopathy = blindness and permanent disability. Retinopathy usually gets better on its own. When it doesn't, cryotherapy and laser therapy can help. Retinal detachment is one of the most severe effects of retinopathy and can be treated with surgery.

Some Scylla-Charybdis. On the one side - death. On the other side - some visual problems that will almost always clear up. What to choose?

Like

EllenHunt 6 days ago

Totally agree!!!

So-called medical "ethics" have gone mad. This is an example. A worse example was the shutting down of the first rotavirus vaccine because of implausible linkage to around 5 intussuception cases. That decision sentenced millions of children to death around the world.

Like

phonenear 6 days ago

This important case certainly is a "teachable moment" and probably is an object lesson in how NIH (and its regulatory arms, OPRR, OLAW, etc) can impede progress toward better treatments, i.e., the mission of the NIH.

What I wish is that in the coverage of the story, there were posted copies of the actual informed consent documents that could be viewed, and some indication of the nature of the verbal discussions of risk that took place. As the NYT coverage correctly noted, the more standard maneuver is to undermine genuine "informed consent" by a C.Y.A. maneuver in which scores of pages of medically specialized verbiage are tossed at the signing individual.

[all of the coverage also makes it look as though the deeper implications of a classic study on EC-IC bypass surgery completely elude Public Citizen and the NIH OPRR, which is a scary and sad notion. Ditto all of the extensive writings on the nature of "informed consent", especially in critical care settings.]

Like

From: Gabrio, Jenna
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; Yvonne Vaucher; Jon.E.Tyson@uth.tmc.edu
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Becky Brazeel; Brenda Vecchio; Cunningham, Meg; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET
Date: Monday, April 29, 2013 10:14:02 AM

A friendly reminder for today's call.

From: Gabrio, Jenna
Sent: Thursday, April 25, 2013 11:35 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET

Dear all,

Thank you all for your quick responses. Please find the call details below and remember that the participant passcode has recently been updated.

The SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in non-enrolled eligible babies has been schedule for:

Monday, 4/29
3:00pm ET

Dial:
Within the USA
(b)(6)

or

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abbot, Michele and Yvonne will be unable to join.

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Wednesday, April 24, 2013 9:14 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.

Please provide your availability for the following dates on the Doodle poll (http://www.doodle.com/48dpg9qq6f8peq8f):

4/25, Th
4/26, F

4/29, M
4/30, Tu
5/1, W
5/2, Th
5/3, F

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Shankaran, Seetha
To: Bell, Edward (Pediatrics); Das, Abhik; Barbara Stoll; Wally Carlo, M.D.; Walsh, Michele; Krisa Van Meurs; Abbot Laptook; Brenda B Poindexter; Fanaroff, Avroy; Ivan Frantz; Goldberg, Ron; Kathleen Kennedy; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; Kurt Schibler; Pablo Sanchez; Richard_A._Ehrenkranz <; paul costello; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Paul Costello
Subject: RE: SUPPORT consent editorial from Iowa City newspaper
Date: Monday, April 29, 2013 9:40:00 AM

Thanks Ed

Very well written

Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Friday, April 26, 2013 9:41 AM
To: Das, Abhik; Shankaran, Seetha; Barbara Stoll; Wally Carlo, M.D.; Walsh, Michele; Krisa Van Meurs; Abbot Laptook; Brenda B Poindexter; Fanaroff, Avroy; Ivan Frantz; Goldberg, Ron; Kathleen Kennedy; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; Kurt Schibler; Pablo Sanchez; Richard_A._Ehrenkranz <; paul costello; Roger Faix; Rosemary Higgins; Paul Costello
Subject: SUPPORT consent editorial from Iowa City newspaper

Here's an editorial that appeared in our local newspaper yesterday.

Ed

Blansfield, Earl (NIH/NICHD) [E]

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Sunday, April 28, 2013 4:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Potential suggestions from today's call

(b)(5) would be great. (b)(5) would also be very good. Others would probably be good too, but only know (b)(5) among them.

Alan

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, April 26, 2013 3:48 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: Potential suggestions from today's call

Let me know if you would think the following folks might be helpful:
The list below are neonatologists in the perinatal section leadership of AAP:

(b)(5),(b)(6)

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, April 26, 2013 2:18 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: FW: revised NIH two pager on Support Study
Attachments: NIH two pager SUPPORT - Revised 042513 1133.docx

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higginsr@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 1:01 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC); Corr, Bill (HHS/IOS)
Subject: revised NIH two pager on Support Study

Hi,
We have made some modest changes to the document on the SUPPORT study. We look forward to continuing the conversation and reaching a good resolution.
Thanks
Kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 11:41 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject: NIH two pager SUPPORT 042413 11PM

Caya,
You asked for a two pager on the support study by 1 pm tomorrow. Please accept our slightly longer (3.15 pages) that has not undergone extensive review here but please know that the nih team is all standing firmly together about our views on this. This is a (b)(5)
kathy

Page 1816 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1817 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1818 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1819 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Luc Brion
To: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie; doctorlevan@gmail.com; "nfiner@ucsd.edu"; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie"s study
Date: Friday, April 26, 2013 2:01:48 PM
Attachments: Proposed Revised Jackie LeVan Protocol 04-26-13.docx

Wally:
Thanks!

Marie;
I added your name to the protocol.
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
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luc.brion@utsouthwestern.edu

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 23, 2013 9:37 AM
To: Luc Brion; Wrage, Lisa Ann; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

We should be careful to add not pre-specified and/or exploratory analyses.

Agree that Marie should be an author.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 9:35 AM
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: Question about Jackie's study

Re: Changes over Time in Therapy and Outcomes Associated with The SUPPORT Trial

I sent you yesterday the proposed revision for the protocol for that study.

May I suggest that Marie Gantz, who contributed so much to the poster, should be listed as a co-author.

I would like everyone's opinion whether additional analyses listed in that protocol, but not yet completed, should be conducted before a first draft of a manuscript.

These analyses include:

1. Using SGA or size for age instead of weight in the multivariate models
2. Building a model incorporating years to assess secular trends; this model could include SUPPORT enrollment as covariate
3. Survey of the 11 participating centers (Page 24)
4. Comparing with another network would be a potential next step; I would not include this in a first manuscript.

Should we have a conference call to review this?

Luc

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UT Southwestern Medical Center

The future of medicine, today.

Application to the NICHD GDB Committee

Changes over Time in Therapy and Outcomes Associated with The SUPPORT Trial

Jaclyn LeVan, DO, Lisa Wrage, Marie Gantz, PhD, Myra Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD, Mambarambath Jaleel, MD, Luc P Brion, MD, Waldemar Carlo, MD, Neil Finer ~~(SUPPORT Subcommittee)~~, MD, Abhik Das, PhD Barbara Stoll, MD, Rose Higgins, MD

For the NICHD Neonatal Research Network

Version 76 ~~- clean~~

9/2/2014 2:55 PM~~5/3/2013 8:57 PM5/3/2013 1:50 PM4/22/2013 3:13 PM11/20/2012 7:55 AM~~

A. ABSTRACT:
We propose an observational study (before/after study design) of GDB data to examine the changes in clinical practices and outcomes in the time period following the results of the SUPPORT Trial.

B. STATEMENT of the PROBLEM
The SUPPORT trial (Finer 2010; Carlo 2010) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The results of the SUPPORT trial were released in May 2010 (Pediatric Academic Societies Meeting) and published in June 2010. The rates of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group, infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7. Among infants with gestational age (GA) 24 0/7 weeks to 25 6/7 weeks, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group.

The rates of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups. However, in the lower oxygen saturation target group, death was significantly more frequent while severe retinopathy of prematurity among survivors occurred significantly less often.

In a retrospective study conducted at Parkland Memorial Hospital, we found that the frequency of DR intubation among GA-matched infants (who did not participate in the SUPPORT trial) decreased significantly in the time period after initiation of the SUPPORT trial (Brion 2008; LeVan 2012).

C. HYPOTHESES:
1. We hypothesize that release of the results of the SUPPORT Trial would be followed by a decrease in frequency of endotracheal intubation in the DR in preterm infants with GA between 24 0/7 and 27 6/7 weeks, and that the decrease in the frequency of DR intubation in each NRN center would depend on baseline rate before the trial.

2. We hypothesize that the release of the SUPPORT trial results would not affect the rate of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age (BPD, defined by O2 requirement at 36 weeks of postmenstrual age), or the rate of death or severe ROP (defined as ROP surgery or retinal detachment).

D. SPECIFIC AIMS:

1. To determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the incidence of endotracheal intubation in the DR in preterm inborn infants

2.To determine the potential impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with GA between 24 0/7 and 27 6/7 weeks, including: incidence of death or BPD at 36 weeks' postmenstrual age (defined by O2 requirement at 36 weeks of postmenstrual age) and incidence of death or severe ROP (defined as ROP surgery or retinal detachment).

E. RATIONALE/JUSTIFICATION:

This study will compare therapy and outcomes in two cohorts of patients reflecting two time periods: one before the SUPPORT Trial, and one after release of the results of the SUPPORT Trial. The study will be limited to the 11 centers that participated in the SUPPORT Trial and were active members of the NICHD NRN during these two periods.

The SUPPORT trial showed no difference in primary outcome between the two respiratory support strategies but advantages of early CPAP on four secondary outcomes: rate of intubation, rate of postnatal steroids for BPD, days of mechanical ventilation among survivors, and rate of being alive and off mechanical ventilation by day 7.

Among infants with gestational age (GA) 24 0/7 weeks to 25 6/7 weeks, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group.

The intubation rate among extremely low birth weight infants (birth weight < 1000 grams) was high (81%) in NRN centers in 1993-1997 (Shankaran 2002). The rate of intubation among patients with GA 24-25 $^{6/7}$ weeks was still high (78%) at Parkland Memorial Hospital in 2005 before starting enrollment into the SUPPORT trial (Brion 2008, LeVan 2012). Because there is substantial heterogeneity in therapy and outcomes across NRN centers, we expect that the change in practice after release of the results of the SUPPORT trial would be inversely related to the baseline rate of intubation in each center. We would expect a decrease in the rate of intubation after the SUPPORT trial in centers that predominantly used intubation in the DR before initiating enrollment, but less change in the rate of intubation in centers that were using higher rates of CPAP before initiating enrollment.

The SUPPORT trial showed no difference in primary outcome between the two oxygen saturation targets, but showed significantly higher mortality and lower rate of ROP with low oxygen saturation target. Specifically the trial showed that targeting lower oxygen saturation resulted in one additional death for approximately every 2 cases of severe ROP prevented. Since the SUPPORT trial is the first trial to show that targeting low oxygen saturation significantly increases mortality in extremely preterm infants, some centers or providers using low oxygen saturation target before the SUPPORT trial might consider increasing their target levels or their alarm limits after releasing the results of the

SUPPORT trial. However several centers or providers may choose to wait instead for the release of long-term data results from the SUPPORT trial and for the results of additional trials (e.g., the BOOST-II UK trial (Johnston 2011).
These data are not collected as part of the GDB. We plan to query the sites using the survey attached to this protocol.

F. BACKGROUND/PREVIOUS STUDIES:

F.1. CPAP vs. endotracheal intubation and surfactant:
Prophylactic and early natural surfactant administration at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in intubated preterm infants who either are at risk for respiratory distress syndrome (< 30 weeks of GA) or have established respiratory distress syndrome (Soll 1997, Soll 1999, Soll 2001). Several studies have suggested a benefit for early CPAP for preterm infants with respiratory distress syndrome, including a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity (Avery 1987, Van Marter 2000, VanPee 2007, Jonsson 1997, Gitterman 1997,) except for an increase in the risk of pneumothorax (summary relative risk 2.36; 95% confidence interval 1.25, 5.54) (Ho 2002). In one observational study, 76% of infants with a birth weight ≤ 1250 g who were initially treated with CPAP did not require intubation within 72 hours (Ammari 2005).

The NICHD Feasibility Trial (Finer 2004) was designed to determine the feasibility of randomizing ELBW infants of < 28 weeks' gestation to CPAP/positive end expiratory pressure (PEEP) or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine DR intubation for surfactant administration. Forty-five percent (47 of 104) of infants < 28 weeks' gestation required intubation for resuscitation in the DR. CPAP/ PEEP in the DR did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life.

Several multicenter randomized controlled trials (RCTs) have compared early CPAP with intubation in the DR. The IFDAS trial (Thomson 2001) showed no significant difference between 4 groups (Elective intubation with surfactant administration and extubation within 2 hrs; early nasal CPAP with selective short intubation for surfactant administration; elective intubation with surfactant administration and artificial ventilation; selective intubation with surfactant administration and artificial ventilation based on clinical criteria) in total respiratory support until estimated date of delivery or discharge home (if earlier) and other neonatal complications. However, this study was not powered for any of the outcomes.

COIN Trial:
The COIN trial (Morley 2008) randomized 610 infants from 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress. Infants were randomized, either to intubation and ventilation, or to CPAP at 8 cm H_20, with intubation for those who met failure criteria. The primary outcome of death or BPD at 36 weeks was similar in the CPAP and in the intubation arms 33.9% vs. 38.9%,

(odds ratio=0.58 to 1.12; P=0.19). Infants randomized to CPAP had a higher frequency of pneumothorax (9.1% vs. 3.0%, p=0.001) and a lower frequency of death or need for oxygen at 28 days (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

CURPAP
Sandri et al randomized 208 25-28 weeks GA infants to assess whether prophylactic surfactant followed by CPAP compared with early CPAP with early selective surfactant would reduce the need for mechanical ventilation in the first 5 days of life (Sandri 2008). They found no difference in the rate of mechanical ventilation during the first 5 days of life, nor in the rate of death and type of survival at 28 days of age or 36 weeks of postmenstrual age.

The Columbian Neonatal Research Network randomized 279 preterm 27-31 week GA infants to either very early surfactant, extubation, and nasal continuous positive airway pressure (treatment group) or nasal continuous airway pressure alone (control group) (Rojas 2009). They found that allocation to the treatment group decreased the need for subsequent mechanical ventilation, and decreased the incidence of air-leak syndrome, but did not affect the rate of chronic lung disease defined as oxygen requirement at 36 weeks of postmenstrual age.

SUPPORT Trial (extracted from Finer 2010 and Carlo 2010):
The SUPPORT trial (Finer 2010; Carlo 2010) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the DR and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The study enrolled 1316 infants.
The primary outcome of the CPAP vs. surfactant trial was the rate of composite primary outcome of death or bronchopulmonary dysplasia (BPD) defined by requirement for oxygen or positive pressure support with CPAP or mechanical ventilation at 36 weeks (with an attempt to remove oxygen in neonates receiving less or equal to 30% oxygen). The rates of the primary outcome (death or BPD at 36 weeks) were not significantly different between the CPAP and surfactant groups (47.8% vs. 51.0%, Relative risk (RR) 0.95 (95% Confidence interval (CI) 0.85, 1.05, adjusting for GA, center and familial clustering). In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.
In post hoc stratified analyses of secondary outcomes, among infants who were born between 24 weeks 0 days and 25 weeks 6 days of gestation, the rates of death during hospitalization and at 36 weeks were significantly lower in the CPAP group than in the surfactant group (rate of death during hospitalization: 23.9% vs. 32.1%; relative risk with CPAP, 0.74; 95% confidence interval [CI], 0.57 to 0.98; P = 0.03; rate of death at 36 weeks: 20.0% vs. 29.3%; relative risk, 0.68; 95% CI, 0.5 to 0.92; P = 0.01.

The Vermont Oxford Network randomized 648 preterm infants to one of 3 approaches to the initial management: prophylactic surfactant followed by a period of mechanical ventilation (prophylactic surfactant [PS]); prophylactic surfactant with rapid extubation to bubble CPAP (intubate-surfactant-extubate [ISX]) or initial management with nasal bubble CPAP and selective surfactant treatment (nCPAP) (Dunn 2011). When compared with the PS group, the relative risk of BPD or death was 0.78 (95% confidence interval: 0.59-1.03) for the ISX group and 0.83 (95% CI: 0.64-1.09) for the nCPAP group. There were no statistically significant differences in mortality or other complications of prematurity. In the CPAP group, 48% were managed without intubation and ventilation, and 54% without surfactant treatment.

Retrospective study at Parkland Memorial Hospital:
A retrospective study (Brion 2008; LeVan 2012) was conducted at Parkland Memorial Hospital to assess the impact of SUPPORT trial initiation in July 2005 on patient management and short-term outcomes in non-participant preterm infants. We analyzed two prospective databases: the resuscitation registry and the neonatal intensive care unit (NICU) database. We included inborn infants with GA < 35 weeks during 3 epochs: 1st epoch before SUPPORT trial (01/03-06/05), 2nd epoch during SUPPORT trial recruitment at Parkland (07/05-02/09), and 3rd epoch after SUPPORT trial recruitment (3/09-6/10)]. We excluded infants who received comfort care only (infants with lethal congenital anomalies or chromosomal abnormalities and GA less than 23 weeks), and those enrolled in the SUPPORT trial.
Among neonates < 28 weeks of GA, initiation of the SUPPORT trial was associated with a significant decrease in the rate of intubation in the DR, and increase in the rate of early intubation (< 4 hours of age) in the NICU, decrease in the rate of surfactant administration for respiratory distress syndrome, an increase in the rate of DRCPAP, and an increase in the rate of pneumothorax but with no change in the rate of death or BPD (defined as O2 requirement at 28 days; physiologic definition of BPD was not in the database in 2003-05 cohort). Most pneumothoraces occurred in patients who were intubated in the DR. In multivariate analysis pneumothorax was associated with epoch and with administration of surfactant for respiratory distress syndrome (RDS). The rate of death or BPD was significantly associated with need for respiratory support (DR intubation, DR CPAP, surfactant for RDS), with low GA and low weight for GA, but not with epoch.

	1st Epoch N=180	2nd Epoch N=230	3rd Epoch N=78	P
DRintubation	78%	55%	60%	<0.0001
DRCPAP	27%	51%	62%	<0.0001
Early NICU intubation	4%	9%	13%	0.02
Surfactant	69%	56%	64%	0.03
Pneumothorax	7%	10%	18%	0.02
Death or BPD	52%	45%	57%	0.26

F.2. Oxygen administration upon admission to the neonatal intensive care unit:
Trials published in the 1950's comparing restricted (≤ 50%, only for clinical indication or

cyanosis) versus unrestricted (routine for 2-4 weeks or until reaching 1500 g) ambient oxygen in very low birth weight infants upon admission or within the first 48 hours showed a significant reduction in ROP and severe ROP (Duc 1992, Askie 2009) without a significant change in mortality (risk difference 4.9%, 95% CI -5.2, + 14.9; risk ratio 1.23, 95% CI 0.80, 1.90). Observational studies have suggested that targeting low oxygen saturation upon admission in very preterm infants may reduce the risk of ROP (Tin 2007) without increasing mortality (Chow 2003, Deulofeut 2007, Wright 2006). No randomized trials until the SUPPORT trial have assessed the effect of targeting different oxygen saturation levels upon admission on morbidity and mortality in very preterm infants.
SUPPORT Trial:
The primary outcome of the oxygen saturation trial component of the SUPPORT trial was a composite of severe ROP (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) and/or death before discharge from the hospital. The rates of the primary outcome of the oxygen saturation trial (severe ROP or death) were not significantly different between the two oxygen saturation target groups (28.3 vs. 32.1%, respectively; relative risk (RR) 0.90; 95% confidence interval (CI) 0.76, 1.06; p= 0.21). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs. 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001). However, in the lower oxygen saturation target group, death was significantly more frequent, while severe retinopathy of prematurity among survivors occurred significantly less often. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

BOOST-II UK trial:
Further analysis of the oxygen saturation algorithm curve used in the SUPPORT Trial showed unexpectedly low frequency of saturation between 87 and 90%, which resulted from merging two separate curves (Johnston 2011). Recruitment into the BOOST-II UK trial (https://www.npeu.ox.ac.uk/boost, accessed 12/12/11) has now been completed. Babies in that trial have been randomized to keep the oxygen saturation level as much as possible in the range 85-89% and in the other group in the range 91-95%.

G. METHOD/PROCEDURES:

Study Design:
We propose a retrospective analysis of the GDB using a before/after design with one cohort of patients born before the date of initiation of the SUPPORT trial in each NRN center (1/1/2003-12/31/2004) and a second cohort of patients starting after release of the results of SUPPORT Trial to NRN centers (1/1/2010-12/31/2012). We propose to use the 11 centers that participated in the SUPPORT trials and in the NRN during the cycles relevant to the two cohorts.

Study Population:
Cohorts:
We propose to analyze patients in the NRN GDB in two successive cohorts. The first cohort includes patients born during a 2-year period preceding the SUPPORT trial (from

1/1/2003-12/31/2004). The second cohort includes patients born after releasing results of the SUPPORT trial (1/1/2010-12/31/2012).

Eligibility and exclusion criteria:
We will use eligibility and exclusion criteria identical to those in the SUPPORT trial.

Entry criteria: Eligible infants are

- 24 0/7th to 27 6/7th weeks at birth by best obstetrical estimate,
- without known malformations
- inborn
- delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study span (2003-2012)

Exclusion criteria:

- Known malformations
- Respiratory support (1st cohort) or medical therapy (2nd cohort) withheld or withdrawn at any time prior to death < 12 hours; we will include patients who died early, but exclude those whose support was either withheld or withdrawn.

The 11 sites participating in the NRN during the two selected cohorts and participating in the SUPPORT trial are:
Case Western
UTSW
Wayne
Emory
Cincinnati
Indiana
Brown
Stanford
Alabama
Houston
Duke

Gestational age strata:
We will analyze the same GA strata as in the SUPPORT trial: 24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks.

Study Intervention:
This is a retrospective study of prospectively collected GDB data with before/after study design comparing preterm infants before the date of initiation of the SUPPORT trial and after releasing results the SUPPORT Trial.

Primary/Secondary Outcomes:
Since this proposal includes several secondary outcome variables, it is likely that some differences will reach a p value < 0.05 just by chance. These analyses will be considered as exploratory.

We selected variables that are included in all the versions of the GDB spanning the 2 cohorts for this study: 2002, 2008 and 2011. For this reason we will not use CPAP in the DR, which is not listed in the 2002 GDB, nor the physiologic definition of BPD, which was defined in 2003.

Primary outcome variables:

The primary outcome variables will be comparisons of data in the 2 cohorts limited to centers participating in the SUPPORT Trial and in the NRN during the entire study span (2003-2012):

a. The use of intubation in DR
b. The incidence of composite of death or BPD at 36 weeks (O_2 requirement at 36 weeks of postmenstrual age). We will not use the physiologic definition of the BPD (Walsh 2003, Walsh 2004), which was not available in GDB in 2003-2004.
c. The incidence of composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital. This outcome is similar but not identical to the primary outcome of the SUPPORT trial
d. Mortality rate before discharge

Comment [L1]: Added by Abhik

~~e.~~ e.

Secondary outcome variables:

- Relationship between baseline intubation rate in each center before initiating enrollment into the SUPPORT trial and the change in intubation rate after releasing results of the SUPPORT trial
- Comparisons of data in the 2 cohorts:
    - BPD (defined by oxygen requirement at 36 weeks)
    - Death or BPD (defined by oxygen requirement at 36 weeks)
    - ~~Mortality rate before discharge~~
    - ROP stage 3 or worse in either eye;
    - ROP plus disease in either eye;
    - ROP intervention
    - Surfactant administration (number of doses is not listed in 2011)
    - DR O2,
    - DR bag and mask ventilation,
    - DR chest compressions,
    - DR epinephrine (other drugs are not listed in 2011 GDB Manual)
    - Apgar scores at 1 min and 5 min
    - Temperature within 60 min of birth
    - Pneumothorax
    - Pulmonary hemorrhage
    - Use of postnatal steroids for BPD
    - Duration of ventilation among survivors;
    - Duration of CPAP among survivors
    - FiO2 at 24 hours
    - Duration of oxygen supplementation among survivors
    - Patent Ductus Arteriosus (PDA),

- PDA requiring a cox inhibitor (indomethacin during either period or ibuprofen during the second epoch),
- PDA requiring surgery
- Severe intraventricular hemorrhage (grade III or IV)
- Early onset sepsis
- Late onset sepsis
- First day full feeds (< 20 ml/kg/day IV [2002] or > 120 ml/kg enterally [2008, 2011])
- Weight at 36 weeks
- Necrotizing enterocolitis (stage 2 or greater)
- Length of stay
- Weight at discharge
- Death under 12 hours
- Death or mechanical ventilation at day 7

- 2nd cohort only:
  - DR CPAP

Additional variables available in the GDB will be collected, including

1. Maternal variables: race/ethnicity, gestational age, diabetes, hypertension, singleton vs. multiple pregnancy, prolonged rupture of membranes, antenatal corticosteroids (betamethasone, any/full course), mode of delivery, antibiotics before delivery
2. Neonatal variables: birth weight, gender

Definition of severe ROP for this study:
Since the definition of severe ROP in GDB changed during the span of this study weare using the following definition for severe ROP for this study.

Severe ROP is defined as "retinal detachment (partial or complete), surgery, or Avastin/Anti-VEGf drug" using questions from NG03 section H 'Ophthalmology'. Specifically, an infant is defined as having severe ROP if:

Using NG03 2002 – for the pre-SUPPORT group born 2003-2004:
H.1.a.1.i. Highest Stage of ROP in right or left eye=4 or 5 (retinal detachment) ***or***
H.3.a.i. retinal ablation performed prior to a threshold diagnosis in Right eye='Y' ***or***
H.3.a.ii. retinal ablation performed prior to a threshold diagnosis in Left eye='Y' ***or***
H.3.b.i. any surgery performed in Right eye=1,2,3,4 ***or***
H.3.b.ii. any surgery performed in Left eye=1,2,3,4.

Using NG03 2008, 2011 – for the post-SUPPORT group born 2010-2012:
H.1.b.1. retinal ablation performed in either eye='Y' ***or***
H.1.b.2. scleral buckle or vitrectomy performed in either eye='Y' ***or***
2008 H.1.b.3.
Other therapies='Y' (? if there are any of these we will look at the specifics to see if these fit the definition) ***or***
2011 H.1.b.3. Avastin or other anti-VEGF drug='Y' ***or***

2011 H.1.b.4.
Other therapies='Y' (? if there are any of these we will look at the specifics to see if these fit the definition) *or*
H.2. =2 - Determined severe ROP (ROP surgery, retinal detachment, Avastin or anti-VEGf) in either eye at status.

Sample Size/Statistical Analysis:
Available sample size:

Data in GDB from January 2002 to December 2004 (DATA AND SAFETY MONITORING PLANS for the SUPPORT Trial) included 4055 infants with a gestational age 24 0/7 – 27 6/7. Assuming 10% exclusions, the first 2-year cohort (1/03-1/05) is estimated to yield approximately 2400 infants for analysis.

The GDB data for 2010 included 1776 inborn infants < 29 weeks gestational age. Therefore we estimate that the second cohort (1/1/10-12/31/12~~1~~) would include approximately 2800 infants. This number would be reduced to 2400 infants taking into account the number of centers which are not included in the current NRN cycle.

Sample size calculations were based on currently available data:

1. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or survival with BPD (O2 requirement at 36 weeks of postmenstrual age) of 67%,
2. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or threshold retinopathy of 50%
3. years 1993-1997 intubation rate of rate of 80% among extremely low birth weight infants (Shankaran 2002).
4. 2002-05 mortality rate of 21% in extremely low birth weight infants (Morris 2008)
5. 2002-05 severe ROP frequency of 20% in extremely low birth weight infants (Morris 2008)
6. These calculations will be readjusted to more recent values once we obtain data from the GDB. Specifically we will review data for the period between the Feasibility Study and the SUPPORT trial, i.e., between February 2003 and January 2005.

For the primary outcome variables, we calculated power using chi-square analysis, a 1.25~~67~~% level of significance (because we have four ~~three~~ primary outcomes) and two-tailed tests. The available sample size (n = 4800, 2400 before SUPPORT versus 2400 after SUPPORT) gives a power > 99% to detect a significant change in DR intubation from 80% to 68% (15% relative risk reduction), a power of 83~~5~~% to detect a change in death or BPD (by physiologic definition) from 50% to 45% (10% relative risk reduction), an a power of 97% to detect a change in death or severe ROP from 67 to 61% (10% relative risk reduction). For multivariate analyses, the sample size is much larger than 10 patients per covariate.

Bivariate analyses:

We will conduct bivariate analyses comparing the cohorts born in the time periods before SUPPORT and after SUPPORT with respect to variables related to mortality and all the outcomes listed above (antenatal steroids, gender, Apgar scores, etc.). Bivariate analyses will be done using chi-square analysis (Mantel-Haenszel chi-square for analyses by gestational age stratum) for categorical variables and using Student t-test or Mann-Whitney test as appropriate for continuous variables.

We hypothesize that releasing results of the SUPPORT trial may have preferentially impacted delivery room intubation rate in centers using infrequent intubation before the trial. For this purpose we will use Cochran-Mantel-Haenszel test to compare the frequency of DR intubation in the first and in the second epoch in two strata: centers with baseline percentage of DR $\geq$ 80% and centers with baseline percentage of DR < 80%.

We will use the survey of the centers to have information in each center about O2 saturation targets in the DR and in the NICU before and after SUPPORT. Assuming some centers decided to change their oxygen saturation targets based on the SUPPORT trial results, we will test whether mortality decreased and the rate of ROP increased in centers changing their oxygen saturation target from low (85 to 89% or lower) during the first epoch to high (e.g., 91 to 95%) during the second epoch, but not in the other centers. Because of the small number of centers, we will not be sufficiently powered for this analysis. Furthermore, it is possible that some centers may have changed their target range to different values from those selected for the SUPPORT trial. As an example, it is possible that some centers may have changed their lower saturation limit only.

Multivariate analyses:

We will use Robust Poisson regression models to obtain adjusted relative risks and 95% confidence intervals (CI) for primary outcomes. We will use general linear models for continuous outcomes, results will be expressed as difference in means and 95% CI. Multivariate models will include NRN ~~We will create logistic regression models to predict primary outcomes based on epoch,~~ center and ~~the prespecified~~ prenatal covariates shown to affect outcomes (gestational age, antenatal corticosteroids, gender, singleton vs. multiple, birthweight by 100 g increment) (Tyson 2008). If there are additional prenatal variables approaching significance ($p < 0.10$) between the two epochs in bivariate analysis we will also include them as covariates; ~~as long as they precede (in time) the outcome variable.~~ race/ethnicity, c/section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, ~~NRN center~~. Postnatal variables will be excluded because not all patients may have been exposed in case of neonatal death.

We will create a model specific for BPD, considering the following potential covariates: intubation in the DR, number of doses of surfactant (<1 vs > 1), FiO2 at 24 hours (>90% vs < 90%), PDA ligation, indomethacin for PDA, late-onset septicemia/ bacteremia (Schmidt 2006, Schmidt 2007, Tyson 1999, Ambalavanan 2008, Fanaroff 1998, Clyman 2009) and intrauterine growth restriction (Mestan 2011, Bose 2009, Lal 2003, Sharma

Comment [L2]: Logistic regression was changed into Poisson to yield RR instead of OR.

Comment [L3]: After discussion with Lisa and Marie

2004). For the latter variable, we will consider a model using assess whether being small for gestational age (birth weight < 10th percentile) or birth weight z score (Bose 2009) is the better predictor.

Comment [MG4]: This uses more information than SGA. Could be fine to include both this and birth weight; an exploration of colinearity and it's effect on the model can be conducted.

~~We will also create models specific for each variable:~~

- ~~For intubation in the DR: Model using as additional variables mode of delivery, and maternal hypertension~~
- ~~For mortality: Model using as additional covariates Apgar score at 1 minute (Shankaran 2002), and temperature upon admission (Laptook 2007)~~
- ~~For death or BPD and for BPD: Model using as additional covariates intubation in the DR, number of doses of surfactant (≤1 vs > 1), FiO2 at 24 hours (≥90% vs < 90%), PDA ligation, indomethacin for PDA, late-onset septicemia/ bacteremia (Schmidt 2006, Schmidt 2007, Tyson 1999, Ambalavanan 2008, Fanaroff 1998, Clyman 2009) and intrauterine growth restriction (Mestan 2011, Bose 2009, Lal 2003, Sharma 2004). For the latter variable, we will assess whether being small for gestational age (birth weight < 10th percentile) or birth weight z score (Bose 2009) is the better predictor.~~

We will use survival analysis to predict in-hospital death using a Cox proportional hazards model adjusted for covariates listed above, using the same methods used in the primary SUPPORT analysis. We will assume, as in the SUPPORT, -that infants who survived to discharge or transfer continued to survive to one year of life.

Limitations and alternatives:

Several data are not collected by the GDB. We plan to send the survey attached to this protocol to sites that participated in SUPPORT. We do realize that such surveys may not help reflect accurately the most common practice in each center. Therefore one alternative may be to not collect data on severe ROP/death.

Before/after study design is limited by confounding variables that may have occurred in addition to the variable of interest. As documented above, several studies in addition to the SUPPORT trial were performed during the time period of study. The two cohorts represent different patient populations separated by five years. Strategies and policies may have changed in the same center between the two epochs, and this process may still be going on at the present time, especially for the oxygen saturation results. For this purpose, we will perform logistic regression analyses as described in the previous section on multivariate analyses.

Prophylactic magnesium administration to women at risk for preterm delivery did not affect the risk of neonatal hypotonia (RR 1.02; 95% CI 0.77 to 1.36; 2444 infants) (Rouse 2008), intubation or resuscitation in the DR (2416 infants) (Rouse 2008), tracheal intubation or epinephrine in the neonatal period (226 infants) (Marrett 2007), or many other neonatal outcomes, but significantly reduced the risk for cerebral palsy (overall RR 0.68; 95% CI 0.54 to 0.87; five trials; 6145 infants) (Doyle 2009). Thus neurodevelopment outcome may be modified by systematic administration of intrapartum

magnesium as prophylaxis of neurodevelopment impairment, which may have been started in some NRN centers in response to recent multicenter trials. We will not use NDI as a variable in this study for two reasons: (1) Neurodevelopmental impairment (NDI) assessment criteria changed in the NRN between the two cohorts, and (2) Only infants with GA<27 weeks were routinely followed during the period of the second cohort, and during the period of the first cohort, only those who were <1000 grams BW.

One exclusion criterion used for the SUPPORT trial, i.e., decision made not to provide full resuscitation, is not listed in the GDB baseline form. We will exclude infants who died prior to 12 hours age and had respiratory or other medical support withheld prior to death as surrogate marker for comfort care.
The primary outcomes of death or physiologic BPD and death or ROP, used in the SUPPORT trial, are not available in GDB. The outcome of physiologic BPD (Walsh 2003, Walsh 2004) is only available in the second cohort in the proposed study. The outcome of ROP as defined in the SUPPORT trial (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) is not available in the GDB. The definitions of ROP changed between 2002 and 2006. We are proposing here to assess the frequency of severe ROP (defined as ROP surgery or retinal detachment).

Some variables cannot be analyzed because they were collected during only one of the two cohorts (e.g., tocolytics, magnesium prophylaxis for neuroprotection).

The small number of centers will limit the power of some analyses as indicated above.

Additional limitations (10/21/12)
The original plan was a logistic regression analysis, which has limited ability to accurately predict changes in absolute risk. Since this is a cohort study, we propose to replace the plan for multivariate analysis, i.e., logistic regression analysis (assessing odds ratios), with a robust Poisson regression in a generalized estimating equation model (assessing relative risk). This will allow us to directly calculate the relative risk (RR) and thus absolute risk change from baseline.

This cohort study with a before-after design is limited by the possibility of secular trends.

For this purpose we propose:
~~1.~~ ~~t~~To extend data collection to include
~~1.1.~~ GDB data in 2012 to increase sample size after dissemination of SUPPORT results.
~~1.2. GDB data during SUPPORT recruitment period (2005-2009) to allow serial time analysis and detect the time of any change with the various stages of SUPPORT (recruitment, dissemination of the results). SUPPORT recruitment led to a selection bias (Rich), therefore excluding patients enrolled into SUPPORT may bias the analyses in the current proposal. On the other hand patients randomized to SUPPORT had a 50:50 chance of being intubated in the delivery room. Therefore we will analyze the data two ways: (1) excluding patients enrolled in SUPPORT, and (2) including all patients, using enrollment to SUPPORT as a covariate.~~
~~1.3. GDB data in 28 28 6/7 weeks to include a control group that was not eligible for~~

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Comment [MG5]: Not necessarily true. They had a 50:50 chance of being randomized to early intubation, but infants randomized to the other group were intubated if necessary for resuscitation.

Comment [MG6]: Since we know that the SUPPORT treatment assignments had a significant impact on at least some of the outcomes of interest, it seems like you would have to adjust for treatment group, not just enrollment in SUPPORT. If that is the case, then you will essentially end up testing for differences between treatment groups and non-enrollment in SUPPORT. This is something the SUPPORT subcommittee has recently voted against doing.

In general, I don't see how including infants born during the SUPPORT enrollment period will help answer the question of whether there were secular trends. Again, since we know the SUPPORT treatments impacted at least some of the outcomes, how can we differentiate between the effect of SUPPORT and the effect of any other trend in treatment/management within the SUPPORT population? And, as is pointed out, those who were not enrolled in SUPPORT were a biased subgroup of the eligible population so it does not make sense to compare them to the pre- and post-SUPPORT groups. For these reasons, I do not think it makes sense to include data collected during the SUPPORT study period in this analysis.

~~SUPPORT, but included in GDB. This is essential to assess whether changes observed during SUPPORT were related to selection bias (as shown by Rich et al).~~

Comment [MG7]: I don't follow the logic of how including 28 week GA infants answers this question.

Comment [lpb8]: I have eliminated this entire section.

2 To compare the results of the primary outcomes and death with another multicenter Neonatal Network.

When all analyses of the data at the NICHD NRN are completed, we plan to submit an abstract and to prepare a manuscript. We will then consider comparing the NRN data with another network. This may potentially lead to another study. We consider asking the Canadian Neonatal Network (CNN) first; if they are not interested in collaborating we will approach the Vermont Oxford Network.

We will request the CNN to provide us with the raw data for DR intubation, severe ROP/death, BPD/death and death, as well as baseline variables.

We will need to use identical variables in the two networks. This will require discussion to make sure that the definitions are identical and may require compromising and possibly eliminating some variables.

We propose to compare between the two networks by conducting the following analyses:

(1) A multivariate analysis using robust Poisson regression in a generalized estimating equation model.

We plan to compare data in the 2 networks using Altman's ~~the~~ interaction test (Altman) which uses the ratio of odds ratio and its confidence interval to compare the relative risk in the NRN and the relative risk in the other network. For this purpose we will use SAS as described by Spiegelman et al (Spiegelman) to compare:

Comment [MG9]: What interaction are you testing?

A. The unadjusted RR in each GA stratum

B. The adjusted RR in all patients together (all strata combined) for each of the most important variables: DR intubation, Severe ROP/death, BPD/death, death.

24-25^{+7} week GA

Yearly Data

Network	Parameter of Assessment	01/03-12/04 (Before SUPPORT)	01/03-12/04 (Before SUPPORT)	01/10-12/11 (After SUPPORT)	01/10-12/11 (After SUPPORT)
NICHD NRN	Intubated in Delivery Room				
	Severe ROP/death				
	BPD/Death				
	Death				
CNN	Intubated in Delivery Room				
	Severe ROP/death				
	BPD/Death				
	Death				

Relative Risk and ~~Interaction Test~~Altman's interaction test

Parameter of Assessment	NICHD NRN Relative risk and 95%	CNN Relative risk and 95% Confidence	~~Interaction test~~Altman's

	Confidence Interval (After vs. Before SUPPORT)	Interval (After vs. Before SUPPORT)	interaction test P Value
Intubated in Delivery Room			
Severe ROP/death			
BPD/Death			
Death			

Comment [MG10]: What interaction are you testing here?

26-27$^{6/7}$ week GA
Yearly data

Network	Parameter of Assessment	01/03-12/04 (Before SUPPORT)	01/03-12/04 (Before SUPPORT)	01/10-12/11 (After SUPPORT)	01/10-12/11 (After SUPPORT)
NICHD NRN	Intubated in Delivery Room				
	Severe ROP/death				
	BPD/Death				
	Death				
CNN	Intubated in Delivery Room				
	Severe ROP/death				
	BPD/Death				
	Death				

Relative Risk and ~~Interaction Test~~Altman's interaction test

Parameter of Assessment	NICHD NRN Relative risk and 95% Confidence Interval (After vs. Before SUPPORT)	CNN Relative risk and 95% Confidence Interval (After vs. Before SUPPORT)	~~Interaction test~~Altman's interaction test P Value
Intubated in Delivery Room			
Severe ROP/death			
BPD/Death			
Death			

Comment [MG11]: What interaction are you testing?

28-28$^{6/7}$ week GA
Yearly data

Network	Parameter of Assessment	01/03-12/04 (Before SUPPORT)	01/03-12/04 (Before SUPPORT)	01/10-12/11 (After SUPPORT)	01/10-12/11 (After SUPPORT)
NICHD NRN	Intubated in Delivery Room				
	Severe ROP/death				
	BPD/Death				
	Death				
CNN	Intubated in Delivery Room				
	Severe ROP/death				
	BPD/Death				

	Death				

Relative Risk and ~~Interaction Test~~Altman's interaction test

Parameter of Assessment	NICHD NRN Relative risk and 95% Confidence Interval (After vs Before SUPPORT)	CNN Relative risk and 95% Confidence Interval (After vs Before SUPPORT)	~~Interaction test~~Altman's interaction test P Value
Intubated in Delivery Room			
Severe ROP/death			
BPD/Death			
Death			

Comment [MG12]: What interaction are you testing?

Adjusted Values for all GA strata combined:

Relative Risk and ~~Interaction Test~~Altman's interaction test

Parameter of Assessment	NICHD NRN Relative risk and 95% Confidence Interval (After vs. Before SUPPORT)	CNN Relative risk and 95% Confidence Interval (After vs. Before SUPPORT)	~~Interaction test~~Altman's interaction test P Value
Intubated in Delivery Room			
Severe ROP/death			
BPD/Death			
Death			

Comment [MG13]: What interaction are you testing?

(2) A run chart using yearly (or 6-month if available) data from 2003 until 2012, to compare trends in the two networks
(3) A multivariate analysis incorporating time into the models to analyze in detail the changes in primary outcomes over time (DR intubation, severe ROP/death, BPD/death, death), to see if there is a sharp decline with the initiation of recruitment into SUPPORT, or after dissemination of the SUPPORT results, or if the long term time trend is more monotonic.

Consenting:
Patients will be selected from GDB using criteria previously explained. We request a waiver for consent form as this research involves minimal risk to patients and collecting data in the GDB has been pre-approved by the IRB in each institution.

Available Population/compatibility with other ongoing protocols
The population available will be those patients in the GDB, corresponding to patients born during the two epochs.

We are not aware of any conflict with other ongoing protocols.

Projected Recruitment Time
Data collection for the proposed study have started in 2012; we propose to extend data collection until the end of 2012.

H. RISKS/BENEFITS:

The benefit will be mostly for the society in that there is potential quality improvement of patient care in NICU. The risk is minimal and included accidental disclosure of medical information which is unlikely.

I. BUDGET:

Cost for access to GDB and SUPPORT database and statistical analysis

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Changes in Therapy and Outcomes Associated with The SUPPORT Trial

Survey - Table of Confounding Variables, rev 10/21/12

	Indication	01/03-01/05	7/12-6/14	Date Started or changed
Prenatal Steroids				
Intrapartum Magnesium use for neuroprotection				
Magnesium use for preeclampsia				
DR cardiac massage or medications				
NeoPuff in DR				
Use of CPAP in DR				
Starting FiO2 in DR				
Use of pulse oximeter in DR to adjust FiO2				
Saturation goals in DR				
Postnatal O2 saturation target range in NICU				
Postnatal O2 saturation lower and upper limits in NICU				
Vitamin A prophylaxis				
Caffeine				
Prophylactic indo-methacin or ibuprofen				
Postnatal Steroids				

From: Laptook, Abbot
To: Abhik Das (adas@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Friday, April 26, 2013 11:11:20 AM

Rose, Abhik

I am meeting with my IRB on Monday and want to appraise them of what is happening across the NRN. Do we have any information from the survey of the other day regarding:

1) Number of centers where any NRN study has been halted
    a. If studies were placed on hold, how many NRN studies were involved
2) If halted, who made the decision
3) If centers are changing their consents for ongoing studies

Per the conference call I plan to look over the LH consent and send some comments to sub-committee members regarding the model consent. Tx, AL

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: SUPPORT consent editorial from Iowa City newspaper
Date: Friday, April 26, 2013 10:19:00 AM

Just did and I sent the second one from the philly paper

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From: Rowe, Mona (NIH/NICHD) [E]
Sent: Friday, April 26, 2013 10:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: RE: SUPPORT consent editorial from Iowa City newspaper

Thanks for sharing. A thoughtful editorial – given all of your interactions lately would you like to share with Kathy before the meeting – I will send to Amy and Sarah

Mona

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, April 26, 2013 10:04 AM
To: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]
Subject: FW: SUPPORT consent editorial from Iowa City newspaper

FYI

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From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Friday, April 26, 2013 9:41 AM
To: Das, Abhik; Shankaran, Seetha; Barbara Stoll; Wally Carlo, M.D.; Walsh, Michele; Krisa Van Meurs; Abbot Laptook; Brenda B Poindexter; Fanaroff, Avroy; Ivan Frantz; Goldberg, Ron; Kathleen Kennedy; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; Kurt Schibler; Pablo Sanchez; Richard_A._Ehrenkranz <; paul costello; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Paul Costello
Subject: SUPPORT consent editorial from Iowa City newspaper

Here's an editorial that appeared in our local newspaper yesterday.

Ed

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Subject: FW: SUPPORT consent editorial from Iowa City newspaper
Date: Friday, April 26, 2013 10:19:00 AM
Attachments: How the feds got it wrong in their critique of a children"s health study - Philly.com.pdf
ATT00001.htm

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From: Krisa Van Meurs [mailto:vanmeurs@stanford.edu]
Sent: Friday, April 26, 2013 10:16 AM
To: Bell, Edward (Pediatrics)
Cc: Das, Abhik; Shankaran, Seetha; Barbara Stoll; Wally Carlo, M.D.; Walsh, Michele; Abbot Laptook; Brenda B Poindexter; Fanaroff, Avroy; Ivan Frantz; Goldberg, Ron; Kathleen Kennedy; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; Kurt Schibler; Pablo Sanchez; Richard_A._Ehrenkranz <; paul costello; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Paul Costello
Subject: Re: SUPPORT consent editorial from Iowa City newspaper

Here's a op ed piece written by Art Caplan and David Magnus from the Philly inquirer.

Krisa

On Apr 26, 2013, at 6:41 AM, "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> wrote:

Here's an editorial that appeared in our local newspaper yesterday.

Ed

<Press-Citizen_editorial.pdf>

How the feds got it wrong in their critique of a children's health study

Featured speaker Dr. Arthur Caplan discusses the ethics of personalized medicine at the First Annual Berkowitz Lecture at the Cooper Medical School of Rowan University on March 5, 2013. (Hillary Petrozziello / Staff Photographer)

POSTED: April 25, 2013

By Arthur Caplan

and David Magnus

GALLERY: Featured speaker Dr. Arthur Caplan discusses the ethics...

The headlines were frightening. Parents had not been properly informed that doctors were putting their extremely premature infants at risk in a study of oxygen treatment. The lead government agency providing oversight to biomedical research said the informed-consent forms did not tell the parents about "reasonably foreseeable risks," which included blindness and death.

This would be a horrific violation of research ethics if it were true. But the truth about this study is far more complicated than the headlines and the government reprimand they were based upon.

When you or your child goes to the doctor and she recommends a treatment, we all like to believe that it will be the best treatment available. The reality is that there are often several treatment options. Different hospitals and doctors favor different drugs, different dosing schedules, different equipment, and even different procedures. Which specific treatment you or your child gets may depend upon who your doctor is or where you happen to live.

In light of this uncertainty, it is imperative to research whether one standardly used treatment is better than the others. Comparative effectiveness research tries to do just that. Yet this is exactly the kind of research that was slammed by government watchdogs and mauled in the press.

The Office for Human Research Protections of the federal Department of Health and Human Services sent a letter to investigators at the University of Alabama at Birmingham blasting the consent form used in a clinical trial to determine appropriate oxygen saturation levels in severely premature neonates. The history of practice in this area is complicated, and the standard of care has varied over the decades. Clinical management of these vulnerable infants is tricky - too much oxygen produces blindness and lung damage, while too little can lead to brain damage and death. It is not clear what levels of oxygen saturation should be the goal, and centers follow different practices.

Neonatologists, to their credit, tried to set up a study that would let them better understand the risks and benefits in the range of oxygen levels being used. University of Alabama investigators took the lead in a large trial to try to get the answers. At all participating institutions, infants were receiving anywhere from low (85 to 89 percent) to high (91 to 95 percent) oxygen levels. Researchers proposed that instead of allowing random or non-evidence-based factors to determine where in that range oxygen

levels were set, infants would be randomized to groups where they got oxygen at the lower and higher ends of what doctors were giving. Since both of these ranges are within the standard of care (85 to 95 percent), many researchers argued that the study they wanted to do carried minimal new risk. Everything they proposed to do with the preemies was already being done, but no one could say what was best.

Federal officials disagree. They claim that limiting the range of oxygen levels, instead of allowing them to randomly range across the spectrum of what is already being tried, alters the risks and benefits to the infants. There is no evidence to support this claim. Any preemie prior to the study could have received oxygen at one of the levels in the study.

Studying treatments to determine which is best is just as important as studying new drugs, vaccines, or devices. In many ways, it is more important, since many more people are exposed to a range of treatments, some of which may be worse or more costly than others. The irony is that the risks in studying treatment are far, far less, since nothing new is being introduced.

The reality is that those regulating research need to update their thinking so as not to scare all of us about this long-overdue and much-needed form of research.

Arthur Caplan is head of the division of medical ethics at New York University's Langone Medical Center. David Magnus is director of the Center for Biomedical Ethics at Stanford University. E-mail them at arthur.caplan@nyumc.org and dmagnus@stanford.edu.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Subject: FW: SUPPORT consent editorial from Iowa City newspaper
Date: Friday, April 26, 2013 10:19:00 AM
Attachments: Press-Citizen_editorial.pdf

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From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Friday, April 26, 2013 9:41 AM
To: Das, Abhik; Shankaran, Seetha; Barbara Stoll; Wally Carlo, M.D.; Walsh, Michele; Krisa Van Meurs; Abbot Laptook; Brenda B Poindexter; Fanaroff, Avroy; Ivan Frantz; Goldberg, Ron; Kathleen Kennedy; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; Kurt Schibler; Pablo Sanchez; Richard_A._Ehrenkranz <; paul costello; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Paul Costello
Subject: SUPPORT consent editorial from Iowa City newspaper

Here's an editorial that appeared in our local newspaper yesterday.

Ed

press-citizen.com

Our View: Informed consent remains a process, a conversation

Written by Press-Citizen Editorial Board Our View

Apr. 25 press-citizen.com

We only can imagine all the bureaucratic hoops that researchers for the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) trial would have had to jump through before they even could begin to ask parents for permission to study the effects of providing lower versus higher concentrations of oxygen on infants born as much as three months early.

After all the study, which lasted between 2005 and 2008, not only had to meet the strict and specific standards that the Office for Human Research Protections — part of the U.S. Department of Health and Human Services — sets in place for all research studies conducted on humans; it also needed to be approved by the independent institutional review boards at all 22 of the research/medical sites where the infants and their families were receiving care.

The University of Iowa Hospitals and Clinics was one of those 22 sites, and 29 of the 1,316 newborns included in the study were seen there.

Each one of those review boards would have its own spin on the federal requirements. And each one also would have been tasked with ensuring that the process by which the researchers gain consent from the parents passes ethic muster.

After all, the study involves gaining consent from a highly vulnerable population — parents whose newborns will not survive without extreme medical intervention. So the researchers would have to be clear that their interests lie in improving the efficacy of the medical procedures for saving all such children.

They would have to be clear that, while the levels of oxygen provided always would be within American Academy of Pediatrics guidelines, those enrolled in the study would be randomized into either the lower range (85 percent to 89 percent) or the higher range (91 percent to 95 percent).

They would have to be clear that they weren't offering any superior treatment for the newborns, that the chances of survival may not be improved by participation in study and that the primary purpose of the study was research, not treatment.

Of course, no matter how clearly the researchers would have explained the study and its purpose, the parents might have heard what they wanted to hear. They might have held out hope for a miracle even as the researchers explained their more sober expectations. (The bioethicists call it the "therapeutic misconception.")

But last month, the oversight coordinator for the Office for Human Research Protections sent a 13-page letter to the University of Alabama at Birmingham, which oversaw the study. The letter said OHRP has determined that the consent document used in the study failed to disclose the full risks involved with limiting oxygen use only to the higher end (a risk of blindness) or the lower end (the risk of death).

The researchers and involved institutions have responded by saying they were upfront about what they knew about the risks at the time. It's because of the data they collected that researchers now know the risks at the lower end are more pronounced than they knew before the study began. And the New England Journal of Medicine printed an editorial and several letters criticizing the OHRP for what they consider a dangerous regulatory overreach.

It would be very unfortunate if medical/research centers were to respond to the letter from OHRP by deciding to make their consent documents longer and filled with even more legalese.

But the issues raised by the SUPPORT study are an important reminder that, whenever researchers are dealing with human subjects, they need to always keep in mind that informed consent isn't just a document; it's a conversation ... a process.

As bioethicist pioneer Jay Katz said a full 40 years ago, "Informed consent would entail, if it is truly seen as an invitation, asking for consent, seeking authorization to proceed, and not making demands under the guise of a symbolic egalitarian gestures. It would necessitate sharing knowledge and admitting ignorance, answering questions and identifying unanswerable questions, appreciating doubts and respecting fears. ... It requires that the interaction between the investigator and the subject become a partnership, giving the subject the right to determine what should be done for and with him, and forcing the investigator to be explicit in what he wants to do and why."

From: Vaucher, Yvonne
To: Gantz, Marie; Susan Hintz; Das, Abhik; Vaucher, Yvonne
Cc: Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Myriam Peralta, M.D.; Wallace, Dennis; Rich, Wade; nancy newman; Bradley.Yoder@hsc.utah.edu
Subject: RE: Antenatal Enrollment vs. Non-enrollment: ND Outcome Poster
Date: Thursday, April 25, 2013 4:52:16 PM
Attachments: Vaucher Antenatal Enrollment PAS 2013-04-24Rev3Final.pptx

All,
Here it is again..... the final "Final" antenatal enrollment poster. I have changed the format to improve the readability but all the data is the same. I will print the poster tomorrow. Thanks for your reviews.
Yvonne

From: Vaucher, Yvonne
Sent: Tuesday, April 16, 2013 4:08 PM
To: Gantz, Marie; Susan Hintz; Das, Abhik
Cc: Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; Laptook, Abbot; mcw3@cwru.edu; Kurt Schibler; ROGER.FAIX@HSC.UTAH.EDU; Myriam Peralta, M.D.; Wallace, Dennis; Rich, Wade; nancy newman; Bradley.Yoder@hsc.utah.edu; Vaucher, Yvonne
Subject: RE: Antenatal Enrollment vs. Non-enrollment: ND Outcome Poster

All,
I know everyone's mind is on the consent debacle, but here is my latest version of the antenatal enrollment a poster which is somewhat relevant to the discussion. I have changed it considerably and have added the adjusted models for death and for NDI (deleting the model for Death or NDI as it is basically identical to the death model). The variables used are the ones in the preceding antenatal enrollment papers. See what you think. I left in the data concerning cognitive scores < 80 since although mild(<80) and severe(<70) cognitive impairment weren't different between the two groups, moderate impairment (<80) was.

Abhik, I changed the conclusion to something between yours and mine as the one you recommended did not seem clear to me and thus potentially not to viewers either. Am certainly willing to work further on the conclusion so it clearly conveys the appropriate message. The essence, I think, is that differences in baseline demographic and neonatal factors, not enrollment in SUPPORT, account for differences in outcome.

Marie, I used the final step of the 3 models for death, NDI and Cognitive score < 80 (1=antenatal, 2=delivery 3=neonatal variables).
Should I carry all the p values out to 3 decimal points?
Also is the 5 minute Apgar < 3 or =3.
Should we put both GA and BW, which are collinear, in the models ? If not, does one or the other become significant in the NDI model? Both are close to significant (BW p=0.06; p=GA 0.08).

In the next analyses we can look at whether enrollment in any of the subgroups independently predicted outcome. I agree with Abhik that this should be carefully thought out with respect to ND outcome.

NICHD NEONATAL RESEARCH NETWORK

Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative?

Yvonne E. Vaucher[1], Susan R. Hintz[2], Wade Rich[1], Marie G. Gantz[3] and Neil F. Finer[1] for the SUPPORT Subcommittee of the NICHD Neonatal Research Network
[1]University of California, San Diego, CA; [2]Stanford University, Palo Alto, CA; [3]RTI International, Research Triangle Park, NC

Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was necessary in order to conduct the trial which included intervention immediately after delivery. Antenatal enrollment was associated with differences in demographic, antenatal and neonatal characteristics between enrolled vs. eligible, non-enrolled preterm infants.

Mothers of eligible/non-enrolled infants were *less likely* to be white/non-Hispanic, insured, have had prenatal care (PNC) or receive antenatal steroids. Rich W, et al. *Pediatrics* 2010;126: e215-0e221

Eligible/non-enrolled preterm infants were *more likely* to have lower gestational age (GA), lower birthweight (BW), and lower Apgar scores, require delivery room resuscitation, develop BPD and severe IVH and die before discharge. Rich W, et al. *Pediatrics* 2012;129:1-5.

The primary, composite neurodevelopmental outcome of SUPPORT was Death or Neurodevelopmental Impairment at 18-22 months corrected age.

To determine whether neurodevelopmental outcomes at 18-22 months corrected age were different for children enrolled in SUPPORT compared to those children who were eligible but not enrolled .

We included all 24-26 week GA infants at Neonatal Research Network sites with birth weight > 400g, born from 1/2006 to 2/2009, who were eligible for SUPPORT. For surviving children a comprehensive neurodevelopmental evaluation was performed at 18-22 months corrected age (CA) using a standardized neuromotor assessment and the cognitive scale of the Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III).

Outcomes compared for the enrolled vs. eligible/non-enrolled children were death, a composite outcome of death or neurodevelopmental impairment (NDI) and levels of cognitive delay. NDI was defined as having a BSID-III cognitive score <70, a Gross Motor Function Classification System Score (GMFCS) ≥2, moderate-severe cerebral palsy (CP), blindness or deafness.

Death or NDI was determined for 95.3% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of the eligible/non-enrolled children.

In unadjusted analyses eligible/non-enrolled children were more likely to:
- -Die before 18-22 months CA (31.7% vs. 24.8%, p <.001),
- -Have composite outcome of Death or NDI (41.4% vs. 33.4%, p<.001)
- -Have a BSID-III cognitive score <80 (19.9% vs. 15.5%, p=.038)

There were no significant differences between enrolled and eligible/non-enrolled children in:
- -NDI (10.4 vs. 12.0%)
- -Components of NDI [GMFCS ≥ 2 (4.8 vs. 6.3%), moderate-severe CP (4.0 vs. 4.9 %), bilateral blindness (1.0 vs. 1.2%), deafness (3.1 vs. 2.3%), BSID-III cognitive score < 70 (7.4 vs. 8.5%) or <85 (26.0 vs. 29.1%)].

After adjustment, antenatal and/or neonatal risk factors, not enrollment in SUPPORT, predicted Death, NDI, Death or NDI and BSID-III cognitive scores <80 at 18-22 months CA as shown in Tables 1-3. Predictors for Death alone were similar to Death or NDI.

Table 1: Enrollment and Statistically Significant Predictors Death or NDI at 18-22 months CA

Effect	OR (95% CI)	p
Enrolled in SUPPORT	0.94 (0.75, 1.16)	0.55
Center	--	<.0001
Gestational age at birth (weeks)	0.64 (0.56, 0.73)	<.0001
Birth weight (100 g)	0.77 (0.71, 0.83)	<.0001
Male	1.8 (1.48, 2.19)	<.0001
Apgar at 5 minutes < 3	2.37 (1.62, 3.47)	<.0001

*All logistic regression models controlled for center, gender, race , gestational age, birthweight, insurance status, at least 1 antenatal visit, antenatal steroids, Apgar scores < 3 at 5 minutes, OR resuscitation with chest compressions and/or epinephrine. Models for NDI and BSID-III cognitive score < 80 also controlled for BPD, (traditional), severe IVH (Grades 3-4) or PVL and severe ROP (surgery or retinal detachment).

Table 2: Enrollment and Statistically Significant Predictors NDI in survivors at 18-22 months CA

Effect	OR (95% CI)	p
Enrolled in SUPPORT	0.96 (0.65,1.43)	0.86
Center	--	<.0001
Male	1.99 (1.37, 2.89)	.0003
BPD	1.94 (1.26, 2.97)	.003
Severe IVH (Grades 3-4) or PVL	3.51 (2.32, 5.31)	<.0001
Severe ROP	1.98 (1.28, 3.07)	.002

Table 3: Enrollment and Statistically Significant Predictors BSID-III Cognitive score < 80 in survivors at 18-22 months CA

Effect	OR (95% CI)	p
Enrolled in SUPPORT	0.81 (0.58, 1.13)	0.22
Center	---	<.0001
Birth weight (100 g)	0.77 (0.68, 0.88)	<.0001
Male	1.79 (1.31, 2.43)	.0002
Antenatal steroids (any)	0.54 (0.34, 0.87)	.011
BPD	1.48 (1.05, 2.09)	.025
Severe IVH (Grades 3-4) or PVL	2.88 (1.98, 4.18)	<.0001
Severe ROP	2.25 (1.54, 3.29)	<.0001

After accounting for baseline demographic and neonatal differences between children enrolled in SUPPORT and those who were eligible but not enrolled, there were no significant differences in death and neurodevelopmental outcomes between the two groups in early childhood.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this poster have been resolved. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug.
Acknowledgements: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University, Case Western Reserve University, Cincinnati Children's Hospital Medical Center, Duke University, Emory University, Indiana University, RTI International, Stanford University, Tufts Medical Center, University of Alabama at Birmingham, University of California - San Diego, University of Iowa, University of Miami, University of New Mexico, University of Rochester, University of Texas Southwestern Medical Center, University of Texas Health Science Center at Houston, University of Utah, Wake Forest University, Wayne State University, Yale University

From: Luc Brion
To: Gantz, Marie; Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie"s study
Date: Thursday, April 25, 2013 3:09:37 PM

Marie;
Thanks a lot and thanks for the discussion.
Hopefully this does not impact the results and is thus not important.
However, if it turns out it is a problem with the data, could we use instead gestational age and size for gestational age (e.g., z score) as was proposed in the protocol?
Luc

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, April 25, 2013 2:02 PM
To: Luc Brion; Wally Carlo, M.D.; Wrage, Lisa Ann; doctorlevan@gmail.com; nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Cc: Gantz, Marie
Subject: RE: Question about Jackie's study

Luc,

I apologize for the delayed response. This week got away from me, but I would be happy to send my thoughts on looking at trends over time next week when I should have more time to think about it.

On the issue of colinearity between GA and BW, although the two are correlated, we can assess whether that is causing a problem in the model by comparing the estimated effect of covariates in models that include one or both variables. When the sample size is large, it is not necessarily a problem to include both in the model, and by doing so you use more of the available information in the data (as opposed to using SGA). I would also caution that the combination of variables you select can lead to interpretability issues. For example, if BW and SGA (but not GA) are included in a model, then SGA can appear protective because, controlling for BW, the better-off babies are those with higher GA (thus, for a given BW, more likely to be SGA).

I will follow up with you again next week as I am out of the office tomorrow.

Marie

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 2:44 PM
To: Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

Wally et al:

Thanks for your email.

I agree with you 100%: we do not consider any pre-specified analyses. All these analyses had been pre-specified in the original protocol.
Lisa, Jackie and I had selected for the poster a set of data from the protocol, which we thought would be the most important for PAS.
The only changes in the protocol I submitted yesterday were those proposed by Lisa, Abhik and Marie during the preparation of the poster, and which have already been incorporated in the results in the poster.

The first analysis in my email today would allow to avoid collinearity between GA and birth weight in all multivariate analyses.
The second analysis addresses secular trends, which is a likely criticism of this manuscript.
The other two analyses are clearly exploratory.

We could definitely stop her and prepare the first draft of the manuscript, or run some of the analyses.

Please let me know what you think.

Best regards,

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, April 23, 2013 9:37 AM
To: Luc Brion; Wrage, Lisa Ann; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: RE: Question about Jackie's study

We should be careful to add not pre-specified and/or exploratory analyses.

Agree that Marie should be an author.

Wally

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, April 23, 2013 9:35 AM
To: Wrage, Lisa Ann; Wally Carlo, M.D.; Gantz, Marie; doctorlevan@gmail.com; 'nfiner@ucsd.edu'; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Barbara Stoll; Pablo Sanchez
Subject: Question about Jackie's study

Re: Changes over Time in Therapy and Outcomes Associated with The SUPPORT Trial

I sent you yesterday the proposed revision for the protocol for that study.

May I suggest that Marie Gantz, who contributed so much to the poster, should be listed as a co-author.

I would like everyone's opinion whether additional analyses listed in that protocol, but not yet completed, should be conducted before a first draft of a manuscript.

These analyses include:

1. Using SGA or size for age instead of weight in the multivariate models
2. Building a model incorporating years to assess secular trends; this model could include SUPPORT

enrollment as covariate

3. Survey of the 11 participating centers (Page 24)
4. Comparing with another network would be a potential next step; I would not include this in a first manuscript.

Should we have a conference call to review this?

Luc

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object
Date: Thursday, April 25, 2013 1:26:00 PM
Attachments: image001.png

Suggestions??

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From: Spong, Catherine (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 1:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object

yes let us start a list - i suggest you i(b)(5)

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:43 PM
To: Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: revised fused thrid and fourth paragraph. please let me know if you object

OHRP may (b)(5) can we get some suggestions together??

Rosemary D. Higgins, MD

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From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object

Thanks.

Also, can NICHD start to pull together a list of folks who are (b)(5) (b)(5) Might be good to look (b)(5) (b)(5)

Sounds like (b)(5) (b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:20 PM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object

Last sentence:
The study enrolled (b)(5) (b)(5)

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From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: revised fused thrid and fourth paragraph. please let me know if you object

(b)(5)

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Celebration of Science at NIH: *watch how medical research saves lives and improves health*

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object
Date: Thursday, April 25, 2013 12:41:00 PM
Attachments: image001.png

Yes
We will get a list together

Rose

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From: Devaney, Stephanie (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:40 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]
Cc: Patterson, Amy (NIH/OD) [E]
Subject: FW: revised fused thrid and fourth paragraph. please let me know if you object

And, can you guys add (b)(5) to that list? Do you know him? He's from Hopkins – Kathy sent herself a note with his name.

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object

Thanks.

Also, can NICHD start to pull together a list of (b)(5)
(b)(5) Might be good to look (b)(5)
(b)(5)

Sounds like (b)(5)
(b)(5) .

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:20 PM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object

Last sentence:
The study enrolled (b)(5)

(b)(5)

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From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: revised fused thrid and fourth paragraph. please let me know if you object

(b)(5)

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Celebration of Science at NIH: *watch how medical research saves lives and improves health*

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Patterson, Amy (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object
Date: Thursday, April 25, 2013 12:36:00 PM
Attachments: image001.png

The range is (b)(5)
(b)(5)

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From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:25 PM
To: Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: revised fused thrid and fourth paragraph. please let me know if you object

Do we (can we) insert a range to specify what we mean by (b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:18 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: revised fused thrid and fourth paragraph. please let me know if you object

(b)(5)

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Celebration of Science at NIH: *watch how medical research saves lives and improves health*

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513 1115
Date: Thursday, April 25, 2013 12:21:00 PM

Bottom line – we (b)(5)

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From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 12:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513 1115

Hi Rose,
Your edits look good to me. With regard to the consent issue, this is one of the difficult concepts to understand among OHRP's comments. I think that because the (b)(5)

(b)(5)

If I have this right, the study was trying to (b)(5)

(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:03 PM

To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: NIH two pager SUPPORT - Revised 042513 1115

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513 1115
Date: Thursday, April 25, 2013 12:14:00 PM

GOOD!

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From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513 1115

No thanks – this was meant to go to Christina

Mona

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:12 PM
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: NIH two pager SUPPORT - Revised 042513 1115

Did you want me to comment on this??

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From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513 1115

I've looked at –haven't seen Rose's (Bob Bock was here too) = =a few but we believe important points to consider -thanks for the opportunity to review

Mona

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Sent: Thursday, April 25, 2013 12:03 PM
To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: NIH two pager SUPPORT - Revised 042513 1115

No virus found in this message.
Checked by AVG - www.avg.com
Version: 2013.0.2904 / Virus Database: 3162/6270 - Release Date: 04/24/13

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Subject: FW: NIH two pager SUPPORT - Revised 042513 1115
Date: Thursday, April 25, 2013 12:12:00 PM
Attachments: NICHD FINAL Congressional Request For NIH Communicationsmr.docx

Did you want me to comment on this??

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301-496-5575
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higginsr@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513 1115

I've looked at –haven't seen Rose's (Bob Bock was here too) = =a few but we believe important points to consider -thanks for the opportunity to review

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 12:03 PM

To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: NIH two pager SUPPORT - Revised 042513 1115

Response Template for Congressional Request on
Communication and Education Activities at NIH

A. Name of your IC or OD Office or Program and Institute/Center/etc. (to be referred to as ICs throughout the template):
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

B. Language that authorizes you to do the communications, education, clearinghouse, etc. work at your IC:

42 U.S.C.284(b)(1)(E), which provides the authorities of the Directors of the National Research Institutes, states that they "may develop, conduct, and support public and professional education and information programs."

42 U.S.C. Sec. 285g (Subpart 7, Section 448 of Public Law 99-158) defines the purpose of the NICHD as "the conduct and support of research, training, health information dissemination, and other programs with respect to gynecologic health, maternal health, child health, intellectual disabilities, human growth and development, including prenatal development, population research, and special health problems and requirements of mothers and children."

42 U.S.C. 285g-4(b)(Public Law 101-613) Congress established the National Center for Medical Rehabilitation Research within the NICHD and included the mandate: "The general purpose of the Center is the conduct and support of research and research training (including research on the development of orthotic and prosthetic devices), the dissemination of health information, and other programs with respect to the rehabilitation of individuals with physical disabilities resulting from diseases or disorders of the neurological, musculoskeletal, cardiovascular, pulmonary, or any other physiological system."

42 U.S.C. 285g-5(c)(E)(Public Law 103-43) NICHD is mandated to develop protocols for training physicians, scientists, nurses, and other health and allied health professionals; conduct training programs for such individuals; develop model continuing education programs for such professionals; and "disseminate information to such professionals and the public" with respect to contraception and infertility research.

Section 1207 of Public law 107-110 states: National Institute for Literacy, in collaboration with the Secretary of Education, the Secretary of Health and Human Services, and the Director of the National Institute for Child Health and Human Development shall—(1) disseminate information on scientifically based reading research pertaining to children, youth, and adults; (2) identify and disseminate information about schools, local educational agencies, and State educational agencies that have effectively developed and implemented classroom reading programs that meet the requirements of this subpart, including those State educational agencies, local educational agencies, and schools that have been identified as effective through the evaluation and peer review provisions of this subpart; and (3) support the continued identification and dissemination of information on reading programs that contain

the essential components of reading instruction as supported by scientifically based reading research, that can lead to improved reading outcomes for children, youth, and adults.

42 U.S.C. 280g-8 (Public Law 110-374) requires the NIH, the CDC or HRSA to make awards for the "establishment of awareness and education programs for health care providers who provide, interpret, or inform parents of the results of prenatal tests for Down syndrome or other prenatally or postnatally diagnosed conditions."

42 U.S.C. 284p(c) (Public Law 111-11) allows the Director of the NIH to provide for a mechanism to "educate and disseminate information on the existing and planned programs and research activities of the National Institutes of Health with respect to paralysis and through which the Director can receive comments from the public regarding such programs and activities." It also includes the provision of support for programs to disseminate information involving care and rehabilitation options and quality of life grant programs supportive of community-based programs and support systems for persons with paralysis and other physical disabilities.

42 U.S.C. 300b-15 (c) (Public Law 110-204), the Hunter Kelly Research Program, encourages the Director of NIH "to include information about the activities carried out under this section in the biennial report required under section 403 of the NIH Reform Act of 2006. If such information is included, the Director shall make such information available to be included on the Internet Clearinghouse established under section 300b-11 of this title."

C. Communications and activities conducted by your office. (You may want to use the list of activities we discussed at the special meeting). If there are items outside your office that are responsive to the request, list them, and explain where they are in your IC. Please be comprehensive and clear (patient recruitment, press, responding to public inquiries, etc.) Any metrics or data about the volume and impact of the efforts would be helpful. (will be used in the overview as examples—it won't be listed by each IC)

- Developed, tested, and produced health information materials and messages intended for parents and caregivers, patients, health care providers and other intermediaries (i.e., educators) to provide evidence-based information about topics within the NICHD mission
- Disseminated research findings to media, researchers, and the public through news releases, Items of Interest, backgrounders:
  - 2010 = 42
  - 2011= 64
  - 2012 = 69
  - 2013 = 20 to date
  - also produced 14 videos on news-related issues since 2010
- Maintain the NICHD Information Resource Center (IRC) that responds to public inquiries and distributes publications:
  - FY2010 (ending 09/30/2010): responded to 62,656 requests and distributed 5,453,693 publications
  - 10/01/2010 through Dec 31 2011 (ending 09/30/2011): responded to 68,611 requests and distributed 3,519,134 publications
  - 2012: responded to 57,289 requests and distributed 3,016,078 publications
  - 2013 to date: responded to 11,789 requests and distributed 1,406,757 publications
- Maintained and redesigned NICHD website with new information and features, including evidence-based health and research information on 75 topics within the NICHD mission intended to replace many of the Institute's printed health publications; developing more thn 30 new topics to match breadth of portfolio; metrics showed that the NICHD website had an ASCI score of 80 for customer satisfaction as of October 2012; since December 1, 2012, the site has had 483,800 visitors and 1,538,599 page views.
- Created NICHD spotlights (web feature articles about NICHD activities) on NICHD research and outreach activities: 95 since 2010
- Exhibited at various public health and health care provider association meetings to disseminate evidence-based health information, highlight emerging scientific advances, and detail breadth of scientific research opportunities with the NICHD mission: approximately 72 since 2010
- Produced 12 monthly Director's podcasts featuring NICHD staff discussing their research and research findings
- Maintained 2 listservs—one for media and one for anyone who wants to learn about NICHD research
- Produced and distributed a monthly e-update to NICHD listservs to highlight Institute spotlights and new research findingss items: 18 thus far
- Developted, maintained, and expand, and continually updateed the national Back to Sleep campaign; changed into the national Safe to Sleep campaign to include new recommendations by the American Academy of Pediatrics related to reducing SIDS and other sleep-related causes of infant death

Comment [MJR1]: Ideally present tense

- Revised 10 publications with the 2011 AAP recommendations and the new campaign identity; drafted content for a Safe to Sleep website
- Worked with communities and organizations to build partnerships and encourage "champions" for safe sleep messages; produced and distributed a video about ways to reduce the risk of SIDS and other sleep-related causes of infant death;
- Created and launched a continuing education program for nurses about SIDS risk reduction and 29,125 nurses have taken the course since it launched in Feb 2010; promoted the nurses CE course with various nursing organizations that were also partners on the course development
- Created and launched a continuing education program for pharmacists about SIDS risk reduction and nearly 300 pharmacists have taken the course since it launched in June 2011; promoted the pharmacist CE course with various pharmacist organizations that also partnered on the course development
- Collaborated with American Indian/Alaska Native organizations to create tailored safe sleep materials for Native communities, which have the highest SIDS rates of any ethnic group in the United States
- Collaborated with Jackson State University, Tougaloo College, the University of Mississippi, and other organizations in Mississippi, which ~~is~~ consistently has one of the top 5 infant mortality rates, to conduct outreach in African American communities in the state to reduce infant mortality

- Launched and maintained the National Child and Maternal Health Education Program, which brings together 32 agencies, professional associations, and organizations interested in maternal and child health, including the American Academy of Pediatrics and the HHS Office of Women's Health
  - ~~Conducted virtual and annual in-person meetings of the steering committee to discuss activities and issues;~~
  - Develop consensus on evidenced-based, public health messages that all organizations can disseminate, multiplying the public health impact of NICHD research findings
  - Produced 3 videos related to reducing elective cesarean before 39 weeks of pregnancy; revised and generated web content~~;~~, which will be shared with women in physician offices throughout the country
  - ~~Disseminated information about "letting baby pick the date of delivery";~~
  - Created a continuing medical education course on reducing late preterm birth and elective cesareans before 39 weeks of pregnancy and posted it on Medscape, where 31,917 total learners took the course
- Maintained and Media-Smart Youth: Eat, Think, and Be Active, an interactive afterschool program for young people aimed at improving media literacy within the context of nutrition and physical activity; evaluated, revised, and produced updated materials
  - Revised facilitator guide, train-the-trainer guide, video segments, collateral materials, and web content;
  - Conducted webinar trainings related to using the materials;
  - Conducted outreach and collaborated with various organizations, including the National Council of Negro Women;
  - Started a grantee program to provide minimal support for orgs that wanted to conduct the program
- Started and maintained an NICHD Facebook page—with 3,351 likes—and YouTube channel, which has 42 subscribers and more than 12,000 video views

Comment [MJR2]: Feels a bit redundant

- Processed FOIA requests, including ~~extensive~~ requests from ~~to meet the needs of~~ corporations, individual researchers, institutions, the national and local media, and a range of ~~national~~ public health and advocacy groups
  - FY 2010 = 43
  - FY 2011 = 31
  - FY 2012 = 52
  - FY 2013 = 38 to date

D. Provide total budget **(not broken out with salary nor FTE, not requested in the letter)** for years 2010, 2011, 2012, and (projected, 2013)

Year	Amount ($)
2010	3,815,944
2011	5,252,115
2012	5,422,849
2013 (Projected)	5,161,693

E. Provide a list **of any communications** contracts you have for each of these years and be sure to include the purpose for each contract. **Please provide a list of the costs each year of each contract.**

Contract	Purpose	Year and Amount
Overall Communications Support	Assist NICHD with media inqueries, ~~news,~~ IRC and inventory management, exhibits, materials and content development, research ~~information~~ dissemination, public health campaigns and programs	2010 = $1,708,900 2011 = $2,333,829 2012 = $2,644,749 2013 (Projected) = $2,506,662
American Indian/ Alaska Native (AI/AN) Infant Mortality Support	Communications, outreach, and information dissemination in AI/AN communities to reduce the risk for SIDS and other sleep-related causes of infant death and other factors associated with infant mortality	2010 = $220,574 2011 = $144,508 2012 = $205,187 2013 (Projected) = $207,948
Mississippi African American Infant Mortality Support	Communications, outreach, and information dissemination in African American communities in Mississippi to reduce the risk for SIDS and other sleep-related causes of infant death and other factors associated with infant mortality	2010 = $250,000 2011 = $250,000
Mississippi African American Infant Mortality Training Support	Training members of African American communities in Mississippi to reduce the risk for SIDS and other sleep-related causes of infant death and other factors associated with infant mortality	2010 = $96,000
Fit for Life Support	Activities related to the dissemination of Media-Smart Youth and WE CAN materials and information with the National Council of	2010 = $35,000

Contract	Purpose	Year and Amount
	Negro Women	
Pharmacist Outreach Infant Mortality Support	Communications, outreach, and information dissemination to and with national pharmacist organizations to reduce the risk for SIDS and other sleep-related causes of infant death and other factors associated with infant mortality	2010 = $99,000 2011 = $99,000
Web Content Development	Support for generating and maintaining content for the NICHD main website and other NICHD-maintained sites, social media and multimedia activities. and other Web-related activities for the NICHD	2011 = $748,357 2012 = $696,711 2013 (Projected) = $724,197
Nurse Outreach Infant Mortality Support	Communications, outreach, and information dissemination to and with national nursing organizations to reduce the risk for SIDS and other sleep-related causes of infant death and other factors associated with infant mortality	2012 = $99,000
Support for Specific Communications Activities	Support for managing web-related activities~~content and content strategy~~, developing news/media items to disseminate research findings	2010 = $99,724 2011 = $364,990 2012 = $364,990 2013 (Projected) = $364,990

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: NIH two pager SUPPORT - Revised 042513 1115
Date: Thursday, April 25, 2013 12:02:00 PM
Attachments: NIH two pager SUPPORT - Revised 042513 1115.docx

Page 1886 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 1888 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: OR and CI for comparing SUPPORT and non-enrolled groups
Date: Thursday, April 25, 2013 11:39:28 AM

Rose,

Abhik asked me to send you the adjusted odds ratio and 95% confidence interval for comparing mortality between infants enrolled in SUPPORT and those eligible but not enrolled. In the model created for the second antenatal consent paper, which adjusted for center, GA, birth weight, gender, race, and antenatal steroids, the OR (95% CI) for death for enrolled vs. non-enrolled infants was 0.88 (0.73, 1.06). The p value was 0.16. Although not statistically significant, the point estimate favored infants who were enrolled in SUPPORT. Let me know if you need any additional information.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-587-5110

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Devaney, Stephanie (NIH/OD) [E]
Cc: Patterson, Amy (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: NIH two pager SUPPORT - Revised 042513
Date: Thursday, April 25, 2013 11:38:00 AM
Attachments: Guidelines for Perinatal Care 7-OXYGEN.docx

See the newest AAP gudielines-
Change the sentence:

(b)(5)

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Thursday, April 25, 2013 11:21 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NIH two pager SUPPORT - Revised 042513

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Thursday, April 25, 2013 10:49 AM
To: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: NIH two pager SUPPORT - Revised 042513

From: Gabrio, Jenna
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; Yvonne Vaucher; Jon.E.Tyson@uth.tmc.edu
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Becky Brazeel; Brenda Vecchio; Cunningham, Meg; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call - 4/29, M, 3:00 PM ET
Date: Thursday, April 25, 2013 11:35:24 AM

Dear all,

Thank you all for your quick responses. Please find the call details below and remember that the participant passcode has recently been updated.

The SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in non-enrolled eligible babies has been schedule for:

Monday, 4/29
3:00pm ET

Dial:
Within the USA
(b)(6)

or

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Unfortunately we couldn't find a time that worked for everyone so Abbot, Michele and Yvonne will be unable to join.

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Wednesday, April 24, 2013 9:14 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.

Please provide your availability for the following dates on the Doodle poll (http://www.doodle.com/48dpg9qq6f8peq8f):

4/25, Th
4/26, F

4/29, M
4/30, Tu
5/1, W
5/2, Th
5/3, F

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: RE: SUPPORT Subcommittee Call - Availability Request
Date: Thursday, April 25, 2013 11:14:00 AM

We need marie so go with the Monday time slot

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Thursday, April 25, 2013 10:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Subcommittee Call - Availability Request

On second thought, maybe it is best if wait until Marie is available on Monday. Is that OK with you?

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Thursday, April 25, 2013 10:54 AM
To: 'Rose (higginsr@mail.nih.gov)' (higginsr@mail.nih.gov)
Subject: RE: SUPPORT Subcommittee Call - Availability Request
Importance: High

Hi Rose,

It looks like the best time for the SUPPORT call might be :

TODAY, 4:00 PM ET (since the NEST surgeon call is cancelled)—missing Kurt, Nancy, Dennis and Marie
TOMORROW - 4/26, F, 3:00 PM ET – missing Marie, Dennis, Abbot, Jon
4/29, M, 3:00 PM ET – missing Abbot, Michele, Yvonne

Please let me know if you would like to have the call today, or if you would prefer another slot.

Thanks,

From: Gabrio, Jenna

Sent: Wednesday, April 24, 2013 9:14 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'; Jon.E.Tyson@uth.tmc.edu
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Becky Brazeel'; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; 'Suzanne Sayers'; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call - Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.

Please provide your availability for the following dates on the Doodle poll (http://www.doodle.com/48dpg9qq6f8peq8f):

4/25, Th
4/26, F

4/29, M
4/30, Tu
5/1, W
5/2, Th
5/3, F

Thanks,
Jenna

Jenna Gabrio, CCRP
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Patterson, Amy (NIH/OD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT 042413 11PM fsc
Date: Thursday, April 25, 2013 11:06:00 AM

The Chow study states (they did not report any information on death):

This study would suggest
that targeted upper limit saturations less than 92% may be
preferable at least with respect to minimizing the risk of ROP.
However, (b)(5)
(b)(5)

Rosemary D. Higgins, MD
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From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 10:51 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT 042413 11PM fsc

Hi Rose,
Sorry for being (b)(5)
(b)(5)
." Would the Tin *et al* study be the appropriate reference?
Amy

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, April 25, 2013 10:43 AM
To: Patterson, Amy (NIH/OD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT 042413 11PM fsc

Rosemary D. Higgins, MD

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From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 10:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: NIH two pager SUPPORT 042413 11PM fsc

Rose,
Please see attached document with highlighted insertion from Dr. Collins. He has asked for a citation; I wasn't sure if the Anderson article in J of Perinatology that you sent this morning was the article we needed to reference or not. Please advise and, if not, send appropriate citations.
Many thanks,
Amy

---

[i] Journal of Perinatology 2004; 24:164–168.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Patterson, Amy (NIH/OD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH two pager SUPPORT 042413 11PM fsc
Date: Thursday, April 25, 2013 10:42:00 AM
Attachments: Anderson J perinatology 2004.pdf

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From: Patterson, Amy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 10:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: NIH two pager SUPPORT 042413 11PM fsc

Rose,
Please see attached document with highlighted insertion from Dr. Collins. He has asked for a citation; I wasn't sure if the Anderson article in J of Perinatology that you sent this morning was the article we needed to reference or not. Please advise and, if not, send appropriate citations.
Many thanks,
Amy

Original Article

Retinopathy of Prematurity and Pulse Oximetry: A National Survey of Recent Practices

Christina G. Anderson, MD
William E. Benitz, MD
Ashima Madan, MD

OBJECTIVE:
To determine if practices related to the use of pulse oximetry in the first 2 weeks following birth and after 2 weeks of age have a relationship to the rate of retinopathy of prematurity (ROP) and retinal ablation surgery in infants ≤ 1500 g.

STUDY DESIGN:
A questionnaire was mailed in July 2001 to 318 neonatal intensive care units (NICUs) in the United States and information was collected regarding SpO_2 guidelines and the rate of both severe ROP and retinal ablation surgery.

RESULTS:
A total of 142 surveys were returned (45%). In all, 87% of the NICUs had SpO_2 guidelines, and 60% of these centers maintained a different range of SpO_2 for infants $\leq$ or >2 weeks of age. The range of SpO_2 was 82 to 100% with an average minimum (min) and maximum (max) of 89 and 95%, respectively. In the NICUs with an SpO_2 max of >98% in the first 2 weeks following birth, the rate of retinal ablation surgery was 5.5 vs 3% in those units with a max SpO_2 >98% ($p<0.05$). After 2 weeks of age, the rate of retinal ablation surgery was 3.3% when max SpO_2 was >92 vs 1.3% when the max SpO_2 was $\leq 92\%$ ($p<0.00001$). The rate of $\geq$ stage 3 ROP after 2 weeks of age was 5.5% when max SpO_2 was >92 vs 2.4% when max SpO_2 was $\leq 92\%$ ($p<0.0005$).

CONCLUSION:
NICUs in the US today have a wide range of SpO_2 guidelines. The results of this survey show a "gradient of risk" towards less retinal ablation surgery when the max SpO_2 is <98% in the first 2 weeks following birth ($p<0.05$). There was a statistically significant lower rate of $\geq$ stage 3 ROP and retinal ablation surgery when the max SpO_2 was $\leq 92\%$ after the first 2 weeks of age. A randomized, controlled trial is needed to establish a safe upper limit of SpO_2 in the premature infant at risk for developing ROP.
Journal of Perinatology (2004) **24**, 164–168. doi:10.1038/sj.jp.7211067
Published online 4 March 2004

Division of Neonatology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA

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INTRODUCTION

Retinopathy of prematurity (ROP) is a retinal neovascular disease that can, in its most severe state, lead to severe vision loss. It is one of the leading causes of blindness in infants ≤ 1500 g in the United States (US), with an estimated 500 infants blinded yearly and another 4500 infants with serious retinal scars.[1,2]

The etiology of ROP appears to be multifactorial and complex. Prematurity with a gestational age <32 weeks and low birth weight (LBW) ≤ 1500 g are two of the known risk factors.[3] Several studies have shown a relationship between oxygen administration and its association with the development of ROP.[4–6] It is hypothesized that the pathogenesis of ROP consists of two phases. During the first phase, normal vasculogenesis is interrupted by the relative hyperoxia of the extrauterine environment, leading to vascular injury and retinal avascularity. The second phase of abnormal neovascularization occurs in response to the relative hypoxia caused by the increased metabolic demands of the developing retina.[7,8] Vascular endothelial growth factor (VEGF), an endothelial-cell specific mitogen, is one of the key angiogenic molecules implicated in the pathogenesis of ROP.[9–11]

In animal models, repeated cycles of hyperoxia and hypoxia have been shown to produce more retinal neovascularization than in those exposed to either hypoxia or hyperoxia alone.[12] However, the arterial oxygen level that constitutes hyperoxia or hypoxia in the premature infant and the required duration of that level in the pathogenesis of ROP remains unknown. Flynn et al.[13] in the early 1990s showed that premature infants in the first several weeks of life with a transcutaneous oxygen tension ($tcPO_2$) ≥ 80 mmHg had an increased incidence and severity of ROP.

The use of pulse oximetry to measure oxygen saturations (SpO_2) has become common practice in neonatal intensive care units (NICUs) since the Flynn study.[14] In addition, there has been a decline in the incidence of ROP from as high as 60 to 21% for any stage.[15] However, a wide variability in the incidence of ROP exists between NICUs at different centers. This may be due to differences in clinical practices as it relates to guidelines of SpO_2 levels. At the time of this survey, there had not been a study in the US comparing SpO_2 guidelines at various centers and the rates of ROP. The purpose of this study was (1) to learn about current clinical practices in US related to pulse oximetry use in LBW infants and (2) to determine if these practices relating to the use of pulse oximetry in the first 2 weeks following birth and after 2 weeks of age had a relationship to the rate of ROP and the rate of retinal ablation surgery.

Journal of Perinatology 2004; 24:164–168

METHODS

A questionnaire was mailed in July 2001 to the directors of 318 NICUs in the US. The list of NICUs was obtained from a roster maintained by Ross Laboratories of all NICUs in the continental US. A cover letter explaining the purpose of the study accompanied the questionnaire. The questionnaire was designed to obtain information about the NICU and patient demographics, SpO_2 guidelines, pulse oximetry devices used, SpO_2 ranges in the first 2 weeks following birth, SpO_2 ranges after 2 weeks of age, the rate of ROP at any stage, the rate of $\geq$ stage 2 ROP, the rate of $\geq$ stage 3 ROP, and the rate of retinal ablation surgery in infants ≤ 1500 g. A second letter and questionnaire was sent 8 weeks later to those individuals who had not returned the initial questionnaire. For analysis, we used the number of respondents for each question. Data are presented as mean ± SEM. Groups were compared using Student's *t*-test.

RESULTS

In total, 144 units returned the survey for a response rate of 45%, representing 45% of all known NICUs in the continental US. There were 98 responses to the first mailing and 46 responses to the second mailing. In all, 85% of the respondents answered the questionnaire completely. The remaining 15% of the respondents answered more than 85% of the questions. There were an equal number of respondents from community-based (59/119) and the university-based NICUs (60/119). Table 1 summarizes the characteristics of the NICUs. A variety of pulse oximetry devices were used (Table 2).

A total of 120 (87%) of the NICUs had documented pulse oximetry guidelines that required a certain SpO_2 range for infants ≤ 1500 g. In total, 18 (13%) of the NICUs did not have specific guidelines, but ranges varied and were dependent on the attending clinician. A total of 69 (58%) of the units with guidelines maintained different SpO_2 guidelines for premature infants in the first 2 weeks following birth than for infants greater than 2 weeks of age. None of the centers maintained a different guideline for infants 2 to 6 weeks of age or between 2 weeks of age and the first eye examination. Few centers maintained different saturations for prethreshold disease.

Table 1 NICU Characteristics

Number of beds	Number of NICUs (%)	Number of patients ≤ 1500 g	Number of NICUs (%)
≤ 20	24 (18)	<50	17 (13)
21–30	29 (21)	50–100	38 (29)
31–40	33 (24)	100–150	35 (26)
>40	51 (38)	>150	43 (32)

Table 2 Pulse Oximetry Devices Used

	Number of NICUs
Nellcor only	74 (54%)
Ohmeda only	20 (15%)
Nellcor and Ohmeda	14 (10%)
Nellcor, Ohmeda, and Massimo	2 (1%)
Nellcor and Massimo	7 (5%)
Massimo only	15 (11%)
Unanswered or did not know	6 (4%)

Table 3 Target Oxygen Saturations

	Minimum SpO_2	Maximum SpO_2
First 2 weeks	89.9±2.7 (82–99)	95.6±1.9 (92–100)
After 2 weeks	90.2±2.3 (82–96)	5.8±1.9 (92–100)
Prethreshold	90.9±2.9 (82–100)	96.2±2.1 (90–100)

Mean ± SD (range).

The range of SpO_2 was 82 to 100% with an average minimum (min) SpO_2 of 89% (±2.7%) and an average maximum (max) of 95% (±1.9%) in the first 2 weeks following birth. Table 3 shows the mean minimum, mean maximum and ranges for target oxygen saturations before and after 2 weeks of age and for prethreshold ROP. There was no statistical difference in the rates of stage 3 ROP in the first 2 weeks after birth for those centers that maintained a maximum $SpO_2 \leq 98\%$ (5.3±0.53%) compared to those centers that maintained a maximum $SpO_2 \geq 98\%$ (8.0±2.4%) ($p = 0.264$). However, the average rate of retinal ablation surgery was higher in those centers that maintained a max $SpO_2 \geq 98\%$ in the first 2 weeks (5.56±1.1 vs 3.07±0.33%, respectively) (Figure 1). As shown in Figure 2, the average rate of ROP $\geq$ stage 3 was greater in those centers if the max SpO_2 was greater than 92% after 2 weeks of age (5.68±0.55% vs 2.49±0.67%, respectively). A similar increase was seen in the average rate of retinal ablation surgery if the max SpO_2 was greater than 92% after 2 weeks of age (3.34±0.34 vs 1.38±0.25%) (Figure 3).

DISCUSSION

Pulse oximetry is a common, noninvasive technique widely used in NICUs to monitor arterial oxygen saturation. It is often used to determine the need and adjustment of supplemental oxygen for critically ill patients. However, the appropriate range of SpO_2 for a premature infant at risk of developing ROP is not clearly defined.

This study presents information on SpO_2 guidelines in NICUs in the US as it relates to the premature infant and the rates of ROP and retinal ablation surgery. The majority of the NICUs who

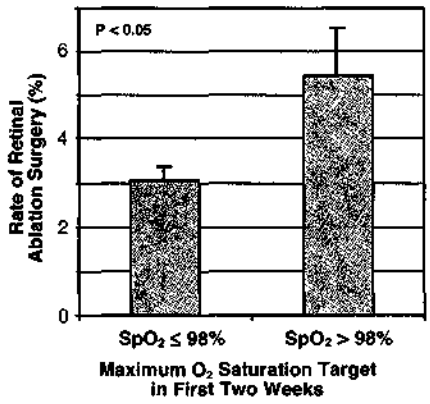

Figure 1. Comparison of rates of retinal ablation surgery between centers with maximum O_2 saturation targets $\leq 98\%$ ($n = 127$ centers, admitting approximately 11,000 infants <1500 g/year) or >98% ($n = 8$ centers, admitting approximately 700 infants <1500 g/year) in the first 2 weeks after birth ($p < 0.05$ by the two-tailed Student's t-test, $t = 2.08$). Values shown represent mean ± SEM.

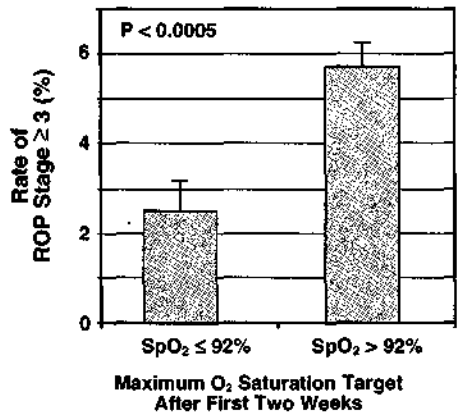

Figure 2. Comparison of rates of ROP ≥ stage 3 between centers with maximum O_2 saturation targets $\leq 92\%$ ($n = 9$ centers, admitting approximately 800 infants <1500 g/year) or >92% ($n = 126$ centers, admitting approximately 11,000 infants <1500 g/year) after 2 weeks of age ($p < 0.0005$ by the two-tailed Student's t-test, $t = 3.70$). Values shown represent mean ± SEM.

responded to the survey have established documented guidelines. There appears to be a wide range of oxygen saturations that are maintained at different centers. Most of the NICUs also maintained different guidelines for the premature infant less than 2 weeks of age than for the premature infant greater than 2 weeks of age. There was no difference in the rates of stage 2 ROP (data not shown).

This study showed a trend towards more retinal ablation surgery at centers where the guidelines for max SpO_2 were $\geq 98\%$ in the first 2 weeks of life. An SpO_2 of 97 to 98% correlates with a PaO_2 of

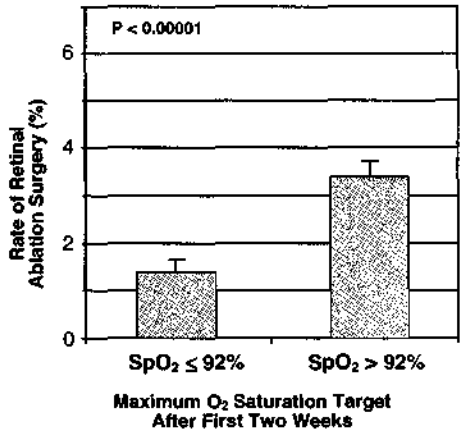

Figure 3. Comparison of rates of retinal ablation surgery between centers with maximum O_2 saturation targets $\leq 92\%$ ($n = 9$ centers, admitting approximately 800 infants <1500 g/year) or >92% ($n = 126$ centers, admitting approximately 11,000 infants <1500 g/year) after 2 weeks of age ($p < 0.00001$ by the two-tailed Student's t-test, $t = 4.71$). Values shown represent mean ± SEM.

approximately 80 mmHg.[16] Therefore, our study concurs with the study by Flynn et al.;[13] infants during the first several weeks of life exposed to longer durations of $tcPO_2 \geq 80$ mmHg had more severe ROP.

Our study also compared SpO_2 guidelines after 2 weeks of age and it was noted that a majority of NICUs maintained different oxygen saturations for their infants during this time. Interestingly, there was a trend towards more advanced ROP ≥ stage 3 and surgery when the guidelines for max SpO_2 were >92%. This oxygen saturation is much lower than seen in the first 2 weeks and correlates with a PaO_2 of 52 mmHg.[16]

In a retrospective review carried out in the United Kingdom, a four-fold increase in severe ROP and the need for cryotherapy was seen when supplemental O_2 was given to maintain an SpO_2 of 88 to 98% in the first 8 weeks of life vs an SpO_2 of 70 to 90%.[17] At the 1 year follow-up, there were four babies registered as blind in the group that maintained 88 to 98% saturation and none in the 70 to 90% saturation group. Furthermore, there was no difference between the two groups in the percentage of infants who survived infancy (52.8 vs 51.6%) or in the incidence of cerebral palsy (16.9 vs 15.4%).

The findings of our survey raise some important issues and questions. First, it is not clear why a majority of NICUs change the parameters for premature infants less than 2 weeks of age and greater than 2 weeks of age. Although this was not a question on the survey, some individuals upon verbal follow-up gave reasons similar to that expressed by Poets;[18] supplemental oxygen leads to an improvement in weight gain, a decrease in airway resistance in infants with chronic lung disease (CLD), and a decrease in the frequency of hypoxemic episodes. Other responders misinterpreted

the results of the STOP-ROP study trial which showed no increase in the risk of progression of ROP in infants with *prethreshold* ROP who were managed with high SpO_2 target ranges of 96 to 99%.[19] However, the STOP-ROP study did not demonstrate the absence of potential adverse effects from widespread application of such strategies, including infants without ROP.

Second, the timing of ROP with the postmenstrual age and not chronological age would suggest that ROP becomes significant when the retina reaches a certain maturity, not the number of weeks after injury to the developing retina.[20] However, only two of the NICUs that responded to the survey had specific SpO_2 ranges for birth weight and gestational age, not chronological age. Perhaps it is this wide range in pulse oximetry guidelines and change in parameters over chronological time seen in clinical practices throughout the US that accounts for the increased rate of ROP seen in this study as well as the variability in incidence of ROP reported by different centers.[15]

In addition, fluctuations in oxygen saturations within a specified min/max range may also contribute to the progression of ROP. A recently published study showed a decline in severe ROP from 12.5 to 2.5% over a 5-year period after the implementation of strict SpO_2 guidelines and adherence of the clinical staff to an educational program enforcing a strict clinical practice of oxygen administration and monitoring.[21] The SpO_2 for the study was 85 to 95% for infants >32 weeks and 85 to 93% for infants $\leq$32 weeks while on supplemental oxygen. The decrease in ROP may have been due to tighter oxygen control decreasing the fluctuations in saturations or possibly due to the lower SpO_2. Several other studies support that it may be the fluctuations between hyperoxia and hypoxia and not the absolute level of arterial oxygenation that are more harmful in the development of severe ROP.[22,23]

The findings of our study do not necessarily support a cause and effect relationship between oxygen saturation guidelines, maximum SpO_2 and the rate of ROP. This was not a randomized, controlled trial; therefore, we do not know if documented guidelines reflect actual clinical practice, that is, what percentage of SpO_2 readings fell within and outside the stated guidelines. Furthermore, the centers who responded to this survey used a variety of pulse oximeters. A variation of 2 to 3% has been reported between some of the different brands.[24] Inconsistent methods for measurement/monitoring of oxygen saturation may obscure potential relationships between target and the risk of development of ROP.

Another limitation of this study was that we did not survey alarm settings. A study performed in 1997 showed that a majority of centers in the US had high alarms set at 100%.[14] Seven of the centers who responded to our survey indicated a maximum SpO_2 of 100% for all infants. Saturations at this level could predispose infants on supplemental oxygen to hyperoxemia.[25] A recent study indicated a systematic bias, worsening as the true saturation deviates from a small range (92 to 97%), with pulse oximetry devices overestimating arterial saturations at low saturations and underestimating at high saturations.[26]

Our questionnaire assumed use of the international criteria for staging of ROP and responses indicated its use.[27,28] Our study also assumed application of retinal ablation therapy for threshold disease as defined in the multicenter trial of cryotherapy for ROP.[29] Despite the limitations, the results of this survey confirm the need for a randomized, controlled trial of oxygen administration, pulse oximetry saturations and the development of ROP.

CONCLUSION

In conclusion, this study shows that NICUs in the US today vary in their pulse oximetry guidelines for premature babies. This variation may contribute to the incidence of ROP. This study would suggest that targeted upper limit saturations less than 92% may be preferable at least with respect to minimizing the risk of ROP. However, a randomized, prospective trial is needed to determine the appropriate O_2 saturations for the very premature infant.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: Sorry if dup
Date: Wednesday, April 24, 2013 7:30:00 PM
Attachments: Anderson 3 perinatology 2004.pdf

Here is the survey article of where NICU's were targeting oxygen saturations (published in 2004)

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 7:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Sorry if dup

Aap doc I have is 2007. What is documentation at start of study that standard of care was 85-95?

Appreciate so much your help

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 10:23 PM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Shurin, Susan (NIH/NHLBI) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: stopped enrollment

Would be great to have (b)(5)

Fc weighed in strongly tonight in (b)(5)
(b)(5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
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kathy.hudson@nih.gov

On Apr 24, 2013, at 9:49 PM, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov> wrote:

I believe that Rose has said (b)(5)
(b)(5)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 9:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Shurin, Susan (NIH/NHLBI) [E]
Subject: RE: stopped enrollment

Non Responsive

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 8:24 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: RE: stopped enrollment

This is from the BOOST II trial. The information from the SUPOPRT trial was confidentially shared with their DSMC (either late 2009, or early 2010 – right after we had our data). No change in the trial enrollment occurred at that time. Their DSMC did a look in December 2010 and halted the study. The investigators wrote the attached letter to the editor which appeared in NEJM in April 2011. These investigators are presenting their data next weekend at the Pediatrics academic societies and I have

attached the abstract which was submitted last November. Publication should be forthcoming. This is the group for which I gave you the consent form.

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From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 8:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: stopped enrollment

Did I hear you or someone else today say that (b)(5)

Blansfield, Earl (NIH/NICHD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 10:18 PM
To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: Fwd: SUPPORT study issue still unresolved
Attachments: NEJM 4-17-13 Editorial.doc; ATT00001.htm

FYI and not to distribute.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
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301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

> **From:** "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>
> **Date:** April 24, 2013, 9:53:48 PM EDT
> **To:** "Corr, Bill (HHS/IOS)" <Bill.Corr@hhs.gov>
> **Subject: SUPPORT study issue still unresolved**
>
> Hi Bill,
>
> I've been taking a (b)(6) but I have learned of a new chapter in an issue that (b)(5) and I need to ask for your assistance.
>
> Sally Howard convened a very important and urgent meeting last Friday between principals of NIH and OHRP, to discuss the issues surrounding informed consent and the SUPPORT study. The study was designed to identify the optimum level of oxygen to administer to extremely premature babies.
>
> The conclusion of the meeting was that (b)(5)
> (b)(5)
>
> Sally is regrettably away, but I understand that in a phone call today between HHS and NIH, OHRP has (b)(5)
>
> The (b)(5) with several editorials appearing from experts that strongly criticize OHRP's position. One example is attached.
>
> Do you have a few minutes early tomorrow to discuss this? I could call anytime before 8:30 AM.
>
> Thanks, and sorry to trouble you,
>
> Francis

NEW ENGLAND JOURNAL OF MEDICINE

EDITORIAL

Informed Consent and SUPPORT

Jeffrey M. Drazen, M.D., Caren G. Solomon, M.D., M.P.H., and Michael F. Greene, M.D.

April 17, 2013DOI: 10.1056/NEJMe1304996

In the summer of 1963, the nation watched in sadness as Patrick Bouvier Kennedy, the youngest child of President John F. Kennedy and First Lady Jacqueline Bouvier Kennedy, was born prematurely and then died of lung disease 2 days later at Children's Hospital in Boston. Even now, it is common knowledge that children born prematurely are at high risk for death.

So it is easy to imagine the stress when, in 2005, your new baby decides to come into the world after only 6 months of gestation, long before your pregnancy has reached term. You know that extremely premature babies like yours may not survive, but you are reassured that you are giving birth at an academic medical center with a sophisticated nursery for premature newborns and with physicians who have extensive experience with very preterm infants. Decades of study and refining practice have resulted in major improvements in the care of premature infants; now most babies weighing a kilogram or more, and many weighing less than this, survive. This progress has come through careful research in multiple aspects of neonatal care, but many questions remain regarding practice that will maximize survival and minimize the long-term sequelae resulting from surviving severe prematurity. Without research studies your neonatologist would simply be guessing about what is best rather than knowing what is best for your child.

The physicians in the nursery ask you to allow your very premature baby to participate in a research study, called the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), part of which is focused on the amount of supplemental oxygen they will give to your baby. They orally explain the study to you and ask you to sign an informed-consent document; it is six pages of single-spaced typescript.

Premature babies often require supplemental oxygen; what was not known in 2005 was exactly how much oxygen to give. The doctors knew that maintaining very high oxygen levels in the blood might cause retinopathy of prematurity (ROP), or abnormal growth of blood vessels in the eyes, which can damage the retinas and impair vision. The informed-consent form notes the higher risk of ROP that is associated with prolonged exposure to supplemental oxygen but states that "the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known" and also notes that "the use of lower saturation ranges may result in a lower incidence of severe ROP." Clinical practice at the time (and that recommended in the 2002 and 2007 guidelines of the American Academy of Pediatrics,[1,2] on whose guidelines committee one of us served) was to target values for the partial pressure of arterial oxygen anywhere between 50 and 80 mm Hg, consistent with oxygen saturations measured by pulse oximetry between 85% and 95%. Among the clinical

questions addressed by SUPPORT was whether targeting the upper or lower end of this range might result in better outcomes for very preterm infants.

The study was conceived in 2003, initiated in 2005, and completed in 2009. Trials addressing the same clinical question were initiated in 2006 in the United Kingdom, Australia, and New Zealand (Benefits of Oxygen Saturation Targeting [BOOST II]), indicating the importance of the question.[3] For a baby not enrolled in any of these trials, the specific range of oxygen saturation targeted within these broader guidelines was left to the discretion of the child's physician, who lacked data to guide decision making.

The consent document for SUPPORT that you have been handed spells this out clearly and succinctly: "The babies in the lower range group will have a target saturation of 85–89%, while the babies in the higher range group will have a target saturation of 91–95%. All of these saturations are considered normal ranges for premature infants." You sign the form, and your child enters the study. The same process was also taking place with parents of newborn extremely premature infants at multiple centers across the country.

After 5 years and more than 1300 babies studied, the data from SUPPORT are published in 2010 in the *Journal*.[4] The data show that, even within the recommended oxygen saturation range, babies with a higher oxygen saturation target had a higher risk of ROP, and those with a lower saturation target had a higher risk of death. With this new information, the investigators in the BOOST II trials in the United Kingdom and Australia review their preliminary data and discover that lower oxygen saturations in their trials are also associated with a higher rate of death.[3] These findings changed medical practice at many centers.

There was no way for you as a parent of a child in SUPPORT to know what the answer would be before your child participated. The study made clear that higher oxygen saturations within the then-recommended range increased the risk of retinopathy but decreased the risk of death. This is how new medical knowledge is gained. The story should have ended there, but it didn't.

In 2011, the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services began an investigation into the informed-consent process used when newborns were enrolled in SUPPORT. Their investigation concluded with a 13-page letter of determination sent to the SUPPORT lead center on March 7, 2013 (provided with a sample informed-consent form in the Supplementary Appendix, available with the full text of this article at NEJM.org). The OHRP reached the following conclusion: "It was alleged, and we determine, that the IRB [institutional review board] approved informed consent documents for this study failed to include or adequately address the following basic element required by HHS [Health and Human Services] regulations at 45 CFR 46.116(a): Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts."

This response is disappointing, because it does not take into account either the extent of clinical equipoise at the time the study was initiated and conducted or that the consent form, when viewed in its entirety, addressed

the prevalent knowledge fairly and reasonably. At the time, as explained in the principal investigator's response to the allegations and in a related letter to the editor in the *Journal*[5] there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants. Through hindsight (and essentially faulting investigators for not informing parents up front of a risk later uncovered by the trial itself), the OHRP investigation has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice.

Clinical research is crucial if we are to advance medical science. Clinical investigators acted in good faith to design a trial to address an important question. An informed-consent document was drafted and approved by institutional review boards of participating centers before the work was begun. The OHRP has a duty to investigate questions of research impropriety, but we strongly disagree with their determination of inadequate informed consent in this case.

The results of SUPPORT have been critical in informing treatment decisions for extremely preterm infants. When babies like Patrick Bouvier Kennedy are born today, their chances of survival to adulthood are greatly improved, thanks to research made possible by thousands of parents and their children. We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article was published on April 17, 2013, at NEJM.org.

Source Information

From the Massachusetts General Hospital, Boston (M.F.G.).

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 8:24 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]
Subject: RE: stopped enrollment
Attachments: NEJMc1101319 tarnow mordi.pdf; BOOST II PAS Abstract.mht

This is from the BOOST II trial. The information from the SUPOPRT trial was confidentially shared with their DSMC (either late 2009, or early 2010 – right after we had our data). No change in the trial enrollment occurred at that time. Their DSMC did a look in December 2010 and halted the study. The investigators wrote the attached letter to the editor which appeared in NEJM in April 2011. These investigators are presenting their data next weekend at the Pediatrics academic societies and I have attached the abstract which was submitted last November. Publication should be forthcoming. This is the group for which I gave you the consent form.

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Subject: stopped enrollment

Did I hear you or someone else today say that (b)(5)

there was no effect on TmP per GFR because at 10 hours the calculation was made on the basis of nonfasting values. At 21 hours, although the TmP per GFR was appropriately calculated, on the basis of fasting values, the serum phosphorous level had returned to baseline. The rise in serum levels of 1,25-dihydroxyvitamin D is probably due to the direct stimulatory effect of calcitonin on renal 1α-hydroxylase.[3] Recently, Gooi et al. reported that osteocytes express the calcitonin receptor and respond to calcitonin with an increase in sclerostin production.[4] Since the primary source of FGF-23 is osteocytes, these findings imply that the decline in FGF-23 levels that we observed in patients with X-linked hypophosphatemia was due to the direct effect of calcitonin on osteocytes in this disease. Our study raises the possibility that calcitonin is a therapeutic option for patients with X-linked hypophosphatemia.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Increased 36-Week Survival with High Oxygen Saturation Target in Extremely Preterm Infants

TO THE EDITOR: Following advice from the Data Monitoring Committees (DMCs), recruitment to the U.K. and Australian Benefits of Oxygen Saturation Targeting (BOOST II) trials has closed early after a joint safety analysis showed higher survival rates at 36 weeks' postmenstrual age in infants born at less than 28 weeks of gestation and randomly assigned to oxygen saturation (SpO_2) targets of 91 to 95% rather than 85 to 89% while breathing supplemental oxygen.

In 2010, outcomes at hospital discharge in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT trial), a randomized trial comparing the same SpO_2 ranges among 1316 infants, were reported in the *Journal*.[1] Infants randomly assigned to the lower target of 85 to 89% had a lower risk of retinopathy of prematurity than did those in the higher target group (8.6% vs. 17.9%; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73; P<0.001), but they also had a lower rate of survival to hospital discharge (mortality, 19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; P=0.04). The U.K., Australian, and New Zealand BOOST II trials were designed to compare SpO_2 targets of 85 to 89% versus 91 to 95%, with a primary outcome of survival without disability at 2 years corrected for gestation. A prospective meta-analysis of all the neonatal oxygen trials is planned.[2] After the results of SUPPORT were published, the DMCs of the other trials separately reviewed their interim data and found no reason to stop recruitment.[3]

In the U.K. and Australian trials, infants have been managed with the use of Masimo oximeters similar to those used in the SUPPORT trial except that, by early 2009, all oximeters were fitted with a revised calibration algorithm.[4] Both the original and revised calibration algorithms perform within the recommended standards for accuracy, but the revised algorithm is associated with improved SpO_2 targeting, more closely resembles the calibration algorithms in other oximeters,[4] and is now the current standard algorithm in Masimo oximeters (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

In December 2010, a joint safety analysis of survival at 36 weeks' postmenstrual age was undertaken, pooling 2315 infants in the U.K., Australian, and New Zealand trials with the 1316 infants in the SUPPORT trial,[1] as provided

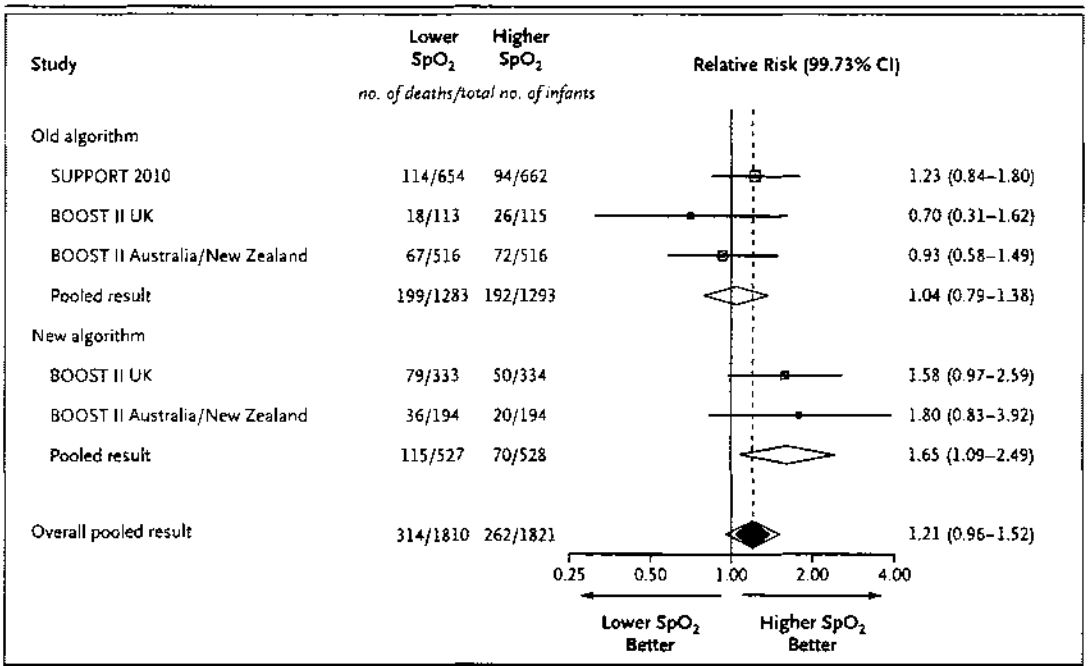

Figure 1. Plot of Survival to 36 Weeks' Postmenstrual Age in 3631 Infants in the SUPPORT and BOOST II Trials According to the Calibration Algorithm Used.

Horizontal lines and open diamonds indicate 99.73% confidence intervals (CIs); the black diamond indicates a 95% CI. The treatment effect with the use of the new versus the old oximeter calibration algorithms is heterogeneous (P=0.006 for interaction in pooled comparisons). The I-squared statistic for all comparisons was 86.5%. The relative risk for the SUPPORT 2010 study was not adjusted for clustering in multiple births.

for in the U.K. protocol.[5] Guidelines prespecified that investigators be told the results if the difference in 36-week survival between groups for all infants, or for those recruited after introducing the new calibration algorithm, exceeded 3 SE (equivalent to 99.73% CI, with P=0.003).[5] Among all 3631 infants, those randomly assigned to an SpO_2 of 91 to 95% had a higher survival rate than those assigned to an SpO_2 of 85 to 89% (mortality, 17.3% vs. 14.4%; relative risk for survival associated with higher SpO_2 target, 1.21; 99.73% CI, 0.96 to 1.52; P=0.015). Among the 1055 infants in the U.K. and Australian trials who were treated after the change in the calibration algorithm, survival differences were greater (mortality, 21.8% vs. 13.3%; relative risk for survival associated with higher SpO_2 target, 1.65; 99.73% CI, 1.09 to 2.49; P<0.001; test for interaction for pooled comparisons of old vs. new algorithm, P=0.006) (Fig. 1). The DMCs reported these results to the trial steering groups. Because of the findings in the 1055 infants on the new algorithm, both trials closed recruitment. Detailed reports on outcomes up to the time of hospital discharge are planned.

Targeting neonatal SpO_2 is imprecise.[4] These data allow no inferences about risks and benefits of other targets. Until longer-term data on survival and morbidity are available, we consider it prudent not to target an SpO_2 of 85 to 89% in infants born earlier than 28 weeks of gestation. Final recommendations await information on the primary outcomes of disability-free survival, anticipated in 2014 (Current Controlled Trials number, ISRCTN00842661 [U.K. trial]; and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 [Australian trial] and ACTRN12605000253606 [New Zealand trial]).[2]

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Supported by the Medical Research Council of the United Kingdom, the National Health and Medical Research Council of Australia, and the Health Research Council of New Zealand.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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5. BOOST-II UK (Benefits of Oxygen Saturation Targeting) Trial. Protocol and handbook. Oxford, England: National Perinatal Epidemiology Unit, February 2011. (https://www.npeu.ox.ac.uk/files/downloads/boost/BOOSTII-Protocol.pdf.)

CORRECTIONS

Case 7-2011: A 52-Year-Old Man with Upper Respiratory Symptoms and Low Oxygen Saturation Levels (March 10, 2011; 364:957-66). In the Causes of Low Oxygen Saturation on Pulse Oximetry subsection of Differential Diagnosis, the unit of measure for wavelengths should have been nm, rather than mm, in two instances: in the first sentence under Hypoxemia (page 959) and in the second sentence of the second paragraph under Dapsone and Methemoglobinemia (page 960). The article is correct at NEJM.org.

Lying Low (Clinical Problem-Solving article, March 3, 2011; 364:871-5, and Interactive Medical Case, February 10, 2011; 364:e10). In the 13th paragraph of the Clinical Problem-Solving article, beginning "A fast was initiated . . ." (page 873), the third sentence should have given the patient's insulin level in μIU per milliliter, rather than mIU per milliliter. In the 10th slide of the Interactive Medical Case, insulin should have been reported in μIU/ml, rather than mIU/ml. Both the article and the interactive case are correct at NEJM.org.

A Syndrome with Congenital Neutropenia and Mutations in *G6PC3* (January 1, 2009;360:32-43). In Table 1 (page 35), the genotype for Patient 8 should have been "c.[778G→C]+[778G→C], p.[Gly260Arg]+[Gly260Arg]," rather than "c.[784G→C]+[784G→C], p.[Gly262Arg]+[Gly262Arg]." In the *G6PC3* Mutations in Other Patients subsection of Results (page 40), the fourth sentence should have begun, "The two other missense mutations . . . ," rather than, "The three other missense mutations . . . ," and the fifth sentence should have read, "None of these additional patients with *G6PC3* mutations had mutations in *ELA2* or *HAX1*, with the exception of a monoallelic genetic variant in *HAX1* (p.Val172Ile) in Patient 10. Monoallelic mutations in *HAX1* have never been associated with congenital neutropenia. Therefore, these three genetic defects represent distinct variants of severe congenital neutropenia," rather than, "None of these additional patients with *G6PC3* mutations had mutations in *ELA2* or *HAX1*, a finding suggesting that these three genetic defects are distinct variants of severe congenital neutropenia." The article is correct at NEJM.org.

NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal's Web site (NEJM.org/medical-conference). The listings can be viewed in their entirety or filtered by specialty, location, or month.

MAYO CLINIC

The following courses will be offered in Rochester, MN, unless otherwise indicated: "Clinical Autonomic Quantitation Workshop" (May 20–22); "Hot Topics in Neurology and Neurosurgery for the Primary Clinician" (June 9 and 10); "Mayo Clinic 20th Annual Internal Medicine Board Review" (June 14–19); "8th Annual EUS Course 2011: Case-Based Pancreatology" (July 20–23); "Radioactive Seed Localized Breast Surgery Workshop" (July 22); and "Rhinofest 2011: Mayo Clinic Comprehensive Course in Rhinology" (Aug. 18–21).

Contact Mayo School of CME, 200 First St. SW, Rochester, MN 55905; or call (507) 284-2509 or (800) 323-2688; or fax (507) 284-0532; or see http://www.mayo.edu/cme; or e-mail cme@mayo.edu.

47TH ANNUAL ROBERT M. JERESATY, M.D., CARDIOVASCULAR SYMPOSIUM

The symposium will be held in West Hartford, CT, May 4 and 5.

Contact the Hoffman Heart and Vascular Institute of Connecticut, Saint Francis Hospital and Medical Center, 114 Woodland St., Hartford, CT 06105-1299; or call (860) 714-4019; or fax (860) 714-8001; or e-mail jwesche@stfranciscare.org.

4TH INTERNATIONAL SYMPOSIUM ON CANCER METASTASIS & THE LYMPHOVASCULAR SYSTEM: BASIS FOR RATIONAL THERAPY

The symposium will be held in New York, May 12–14.

Contact CancerMets Symposium, c/o Paradigm Medical Communications, 523 Route 303, Orangeburg, NY 10962; or call (845) 398-5100, extension 20; or e-mail cancermets@paradigmmc.com; or see http://www.cancermets.org.

JOEL AND BARBARA ALPERT LECTURE IN GENERAL PEDIATRICS

The lecture, entitled "Bending the Disparities Curve," will be held in Boston on May 19.

Contact Melissa Brennan, Boston University School of Medicine, 771 Albany St., Suite 3509, Boston, MA 02118; or call (617) 414-7424; or fax (617) 414-3833; or e-mail melissa.brennan@bmc.org.

INTENSIVE BIOETHICS COURSE 37

The course will be offered in Washington, DC, June 6–10.

Contact the Joseph and Rose Kennedy Institute of Ethics, Healy Hall, 4th Floor, Georgetown University, Washington, DC 20057; or call (202) 687-8099; or see http://kennedyinstitute.georgetown.edu/programs.

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[2180.8] Outcomes at Hospital Discharge in the BOOST II Trials of Neonatal Oxygen Saturation Targeting

Benjamin Stenson, William Tarnow-Mordi, Brian Darlow, Peter Brocklehurst, Colin Morley, Peter Davis, Ed Juszczak, Andy King, Lex Doyle, Karen Simmer. Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; University of Sydney, Sydney, Australia; University of Otago, Christchurch, New Zealand; National Perinatal Epidemiology Unit, Oxford, United Kingdom; Royal Women's Hospital, Melbourne, Australia; University of Western Australia, Perth, Australia.

BACKGROUND: Five RCTs are comparing the effects of targeting oxygen saturation (SpO_2) ranges of 85 - 89% vs 91 - 95% on disability-free survival in infants <28 weeks gestation, using masked, offset Masimo oximeters. Interim analysis of the 3 BOOST II trials showed that the high target increased 36 week survival in infants managed after the oximeter calibration software had been revised.[1]
OBJECTIVE: Report outcomes to hospital discharge overall and with old or new oximeter software.
DESIGN/METHODS: Pooled analysis of hospital outcomes.
RESULTS: Overall, targeting 91-95% increased ROP and decreased surgical or fatal NEC. Mortality was not significantly different. There was significant heterogeneity in the effect of oxygen targets on mortality between old and new oximeter software (p = 0.006 on test for interaction), but not for other outcomes. In infants managed with oximeters using new software, targeting 91-95% increased survival (p = 0.001), but had no significant effect on ROP treatment or O_2 treatment at 36 weeks.

Hospital outcomes of infants by SpO_2 target overall				
	SpO_2 85-89%	SpO_2 91-95%	Relative Risk (95% CI)	p value
Death in hospital	235/1219 (19.3%)	202/1217 (16.6%)	1.16 (0.98 - 1.38)	0.09
Treated for ROP	110/1125 (9.8%)	141/1124 (12.5%)	0.78 (0.62 - 0.99)	0.04
Severe IVH	140/1203 (11.6%)	126/1211 (10.4%)	1.12 (0.89-1.40)	0.33
Surgical or fatal NEC	127/1222 (10.4%)	97/1223 (7.9%)	1.31 (1.02-1.69)	0.04
O_2 dependency at 36 weeks	394/998 (39.5%)	461/1031 (44.7%)	0.88 (0.80 - 0.98)	0.02

Hospital outcomes of infants pooled by old vs new oximeter calibration software						
	old software			new software		
	SpO_2 85-89%	SpO_2 91-95%	Risk Ratio (95% CI)	SpO_2 85-89%	SpO_2 91-95%	Risk Ratio (95% CI)
Death in hospital	98/629 (15.6%)	109/630 (17.3%)	0.90 (0.70 - 1.16)	137/590 (23.2%)	93/587 (15.8%)	1.47 (1.16 - 1.86) §
Treated for	52/574	61/562	0.83	58/551	80/562	0.74

ROP	(9.1%)	(10.9%)	(0.59-1.19) ‖	(10.5%)	(14.2%)	(0.54-1.02) ¶

†evidence of highly significant heterogeneity of treatment effect between old vs new software, (test for interaction p=0.005). p = 0.41 §p = 0.001, ‖p=0.31, ¶ p=0.061.
CONCLUSIONS: Targeting saturation 91-95% was associated with survival advantage. Whilst awaiting 2 year follow up it appears wise to avoid a saturation target of 85-89% in infants <28 weeks gestation.
1. Stenson B, et al. N Engl J Med 2011; 364: 1680-2.

E-PAS2013:2180.8

Session: Platform Session: Neonatal Clinical Trials II: Respiratory Management & Outcomes (8:00 AM - 10:00 AM)
Date/Time: Sunday, May 5, 2013 - 9:45 AM
Room: Ballroom C - Walter E. Washington Convention Center
Course Code: 2180

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Subject: RE: NIH memo on SUPPORT study

Amy et al -- You can also use this last QA below.

What are the implications of the SUPPORT study findings?

The SUPPORT findings have already begun to change clinical practice. Based on the study findings, the American Academy of Pediatrics has begun developing guidelines on the use of on invasive ways to administer oxygen to premature infants starting at birth. In addition, based upon what we hearing from the field and seeing in practice, preliminary trends indicate that physicians treating very premature infants are using higher saturation rates to increase improve overall outcomes for these fragile infants. Efforts are being made to collect data on verify these trends.

If you need information in another format and laying out the points differently- I was trying to take a stab at that. I have a very rough draft of that, which I was going to send to Rose – however if what you have for now is adequate, let us know.

Mona

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Subject: RE: NIH memo on SUPPORT study

This is a document that we had previously worked on at NICHD– the issues at hand is that the AAP Guidelines for Perinatal Care were to target sats 85-95%. Thus, since a clinical guideline, there was not evidence at either end that mortality was at issue.

Let me know if you need more documentation.

Thanks for your help
Rose

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Sent: Wednesday, April 24, 2013 5:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH memo on SUPPORT study

We don't really have a template and not enough time to develop one so send whatever you have rose and amy and I will work to get something ready to send downtown

---

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 5:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: Re: NIH memo on SUPPORT study

Amy-
Do you have a template?
Thanks
Rose
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 05:34 PM
To: Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: NIH memo on SUPPORT study

That one pager can now be 2 but can I get a draft tonight???

From: Lewis, Caya (HHS/IOS)
Sent: Wednesday, April 24, 2013 5:32 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: NIH memo on SUPPORT study
Importance: High

Kathy,

Thanks for your time earlier today on this.

(b)(5)

Thanks,

Caya

Caya B. Lewis, MPH
Counselor for Science & Public Health
Office of the Secretary, DHHS

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: Sorry if dup
Date: Wednesday, April 24, 2013 7:13:00 PM
Attachments: HIC-OHRP 2002 Perinatal Guidelines 5th Ed.pdf
CHow.pdf
Tin oxygen article.pdf

Attached are the previous guidelines from 2002- they do not give exact saturation targets. At the time the study started, the NICU's in the network were using the target sat range of 85-95%. The 2007 guidelines from AAP were being formulated based on the Tin and Chow papers (also attached).
Let me know if you need more info
Thanks for all your help
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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higginsr@mail.nih.gov

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 7:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Sorry if dup

Aap doc I have is 2007. What is documentation at start of study that standard of care was 85-95?

Appreciate so much your help

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study
Date: Wednesday, April 24, 2013 6:24:00 PM

In an effort to comply with the needed information, please feel free to copy Kathy Hudson's folks also. They have the big picture

Thanks
Rose

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higginsr@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 6:15 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study

_ thanks for sharing -- I think that they may need something different – was going to work on an outline and send to you shortly

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 6:14 PM
To: Rowe, Mona (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study

This is accurate – working with Kathy and Amy on a note for downtown – I copied you on the email I sent them a few minutes ago.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Rowe, Mona (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 6:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Bock, Robert (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study

HI Rose Can we say something like this?

(b)(5)

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,

Analysis and Communication
Eunice Kennedy Shriver National Institute of
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National Institutes of Health, DHHS
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31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 5:48 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study

This is a document that we had previously worked on at NICHD– the issues at hand is that the AAP Guidelines for Perinatal Care were to target sats 85-95%. Thus, since a clinical guideline, there was not evidence at either end that mortality was at issue.

Let me know if you need more documentation.

Thanks for your help
Rose

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From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 5:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH memo on SUPPORT study

We don't really have a template and not enough time to develop one so send whatever you have

rose and amy and I will work to get something ready to send downtown

---

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 5:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: Re: NIH memo on SUPPORT study

Amy-

Do you have a template?

Thanks

Rose

Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 05:34 PM
To: Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: NIH memo on SUPPORT study

That one pager can now be 2 but can I get a draft tonight???

From: Lewis, Caya (HHS/IOS)
Sent: Wednesday, April 24, 2013 5:32 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: NIH memo on SUPPORT study
Importance: High

Kathy,

Thanks for your time earlier today on this.

(b)(5)

Thanks,

Caya

Caya B. Lewis, MPH
Counselor for Science & Public Health
Office of the Secretary, DHHS

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study
Date: Wednesday, April 24, 2013 5:47:00 PM
Attachments: Final Support Internal.docx

This is a document that we had previously worked on at NICHD– the issues at hand is that the AAP Guidelines for Perinatal Care were to target sats 85-95%. Thus, since a clinical guideline, there was not evidence at either end that mortality was at issue.

Let me know if you need more documentation.

Thanks for your help
Rose

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From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 5:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH memo on SUPPORT study

We don't really have a template and not enough time to develop one so send whatever you have rose and amy and I will work to get something ready to send downtown

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 5:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: Re: NIH memo on SUPPORT study

Amy-
Do you have a template?
Thanks
Rose
Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 05:34 PM
To: Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
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Subject: FW: NIH memo on SUPPORT study

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To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: NIH memo on SUPPORT study
Importance: High

Kathy,

Thanks for your time earlier today on this.

(b)(5)

Thanks,

Caya

Caya B. Lewis, MPH
Counselor for Science & Public Health
Office of the Secretary, DHHS

What is the SUPPORT Study?

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) study was a large clinical trial that sought to determine how best to deliver oxygen to very small preterm infants and determine the ideal oxygen saturation targets for these very fragile newborns. The study compared the traditional means of providing oxygen, ventilator therapy with surfactant, to continuous positive airway pressure (CPAP), in which air is blown through a preterm infant's nostrils to gently inflate the lungs. When the study began, the standard treatment was to maintain oxygen levels in the range of 85 to 95 percent. The researchers sought to identify within this standard range the percentage of oxygen saturation that would minimize the risk of retinopathy of prematurity. Previous studies had shown that prolonged exposure to high levels of oxygen could increase the risk of retinopathy of prematurity, a complication of oxygen therapy that affects the retina and can sometimes result in vision loss. The study was divided into two arms, each of which proceeded at the same time, in the same group of infants. In the first arm, each infant had a 50 percent chance of receiving higher oxygen target saturation levels, and a 50 percent chance of receiving lower levels. In the second arm, each infant had a 50 percent chance of receiving oxygen by CPAP and a 50 percent chance of being assigned to the ventilator group.

What did the SUPPORT Study find?

The researchers found that the higher range increased the chances of survival but also increased the chances for ROP. This unexpected but critical finding informed clinical practice. The researchers also concluded that CPAP therapy was as effective as ventilator therapy, and resulted in fewer complications.

How did mortality rates from the study compare to those of infants not in the study?

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

Percent Mortality:	
Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

Had the researchers anticipated a lower survival rate for the infants in the lower oxygen range?

No. The finding of a lower survival rate for those at the lower range was not anticipated or expected. At the time of the study, clinical practice for providing oxygen to very preterm babies varied widely. A target range of 85-95 percent was generally standard clinical practice and in 2007 was recommended by the American Academy of Pediatrics. In fact, at the time, emerging research showed that providing oxygen at the lower end of the acceptable range reduced the

risk of retinopathy without increasing the risk of death and neurodevelopmental impairment. As a result, physicians were starting to use the lower oxygen range to treat very preterm babies.

Has the Office for Human Research Protections (OHRP) criticized the design or rationale for the study?

It is critical to note that the treatments or the rationale of the study has never been in question by the Office for Human Research Protections.

What had OHRP objected to?

The OHRP cited the study for not including language, specifically in the risk/benefit section of the consent form, about research conducted in the 1950s suggesting the risk of death was higher with oxygen restriction.

Why had the researchers not included this language?

The older ROP studies were conducted before the widespread use of ventilators, pulse oximetry, and other sophisticated oxygen monitoring and measurement devices. The risk/benefit description under the oxygen saturation section of the consent form included language that reflected the available information/knowledge/data the oxygen administered at the lower saturation range reduced the risk of retinopathy. Since the current research had not shown a higher risk of death and neurodevelopmental impairment at any of these saturation levels (85-95%), the study authors did not list death and neurodevelopmental impairment as potential risks.

Were parents adequately informed of the study risks?

In addition to the consent form, representatives of the study explained the purpose of the research and its potential risks and benefits to parents and responded to their questions and concerns.

Has the OHRP expressed any additional concerns with the study?

In an interview with the New York Times (but not in the original letter to the Principal Investigator's institution, the University of Alabama), the Director of OHRP, Jerry Menikoff said: "Based on their very hypothesis, they were thinking that there might well be a difference...Being in the higher end [of the oxygen saturation range] should have put you at greater risk of developing eye disease." The parents were informed in the consent form that their children would be assigned at random to the higher or lower range. They were also told that they believed children at the lower range would be less likely to develop ROP. However, it was not explicitly stated that children at the higher range might be more likely to develop ROP.

In addition to the consent form, were there any other safeguards to ensure that the infants would receive the optimal care?

Attending physicians were allowed to override the settings if they thought their patients were in danger, and provide either more or less oxygen if they thought that following either course was in their patients' best interest. In addition, attending physicians and parents were free to ask that their children be withdrawn from the study at any time.

What is the purpose of the Neonatal Research Network (NRN)?

The NRN, which is currently composed of 18 medical research institutions, was established in 1986 to conduct clinical trials and observational studies in neonatal medicine to help reduce infant morbidity and mortality, and promote healthy outcomes.

Consistent with this mission, between 2000 and 2009, deaths of preterm infants declined 5.5%, from 109.75 per 1,000 live births to 103.48. Death rates for "early" preterm infants, those born before 32 weeks, declined 4.9% from 180.95 to 172.15 per 1,000 live births. In addition, NRN findings have helped to change clinical practice and improve outcomes for premature infants, such as:

- ✓ Identifying a safe way to protect newborns whose brains were getting insufficient oxygen
- ✓ Showing that providing additional Vitamin A to infants under 1,000 grams significantly reduced their risk of death or getting chronic lung disease
- ✓ Showing that giving intravenous immune globulin to reduce hospital-acquired infections in very low birthweight infants, actually increased rates of an often fatal intestinal condition in newborns
- ✓ Showing that giving additional glutamine, an amino acid, to extremely low birthweight infants did not reduce their risk of death or sepsis

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT PAS abstract presentations
Date: Wednesday, April 24, 2013 3:23:00 PM

This would be for anyone associated with the study and NIH staff folks

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 3:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT PAS abstract presentations

What? Listed as the presenters?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 3:22 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT PAS abstract presentations

All of the listed folks

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Bock, Robert (NIH/NICHD) [E]

Sent: Wednesday, April 24, 2013 3:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT PAS abstract presentations

For whom? NIH staffers? Or for the presenters?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 3:15 PM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: Re: SUPPORT PAS abstract presentations

Can we generate some talking points for commonly asked questions?
Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Bock, Robert (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 03:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: RE: SUPPORT PAS abstract presentations

OK. None of the presenters are federal employees, correct?

This means they are not obligated to check with us before speaking with reporters. We always (b)(5)
(b)(5) ut they are under no legal obligation to do so and are not required to get our approval in advance for any press contacts they receive.

Having said that, I would (b)(5)
(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 9:09 AM
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: SUPPORT PAS abstract presentations

Bob
The Stevens one is a platform (10 min presentation, 5 min for questions). The other two are poster presentations – the authors stands by the poster for 2-3 hours and fields questions.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Finer, Neil
To: Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu
Subject: Re: risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.
Date: Wednesday, April 24, 2013 2:40:06 AM

I asked on the Phone if we could schedule one
I think everyone was focused on other issues
I will ask Rose to set up a call
Neil

Sent from my iPhone

On Apr 23, 2013, at 10:32 PM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu> wrote:

> Don't you want to call a subcommittee call?
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, April 23, 2013 1:35 PM
> To: Gantz, Marie; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Wallace, Dennis; michele.walsh@UHhospitals.org
> Cc: Rich, Wade
> Subject: RE: risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.
>
> Thanks Marie
> This is at least a slightly bigger number and I agree with your thoughts about their differences from enrolled infants
>
> Neil
>
> -----Original Message-----
> From: Gantz, Marie [mailto:mgantz@rti.org]
> Sent: Tuesday, April 23, 2013 4:47 PM
> To: Finer, Neil; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Wallace, Dennis; michele.walsh@UHhospitals.org
> Cc: Rich, Wade
> Subject: RE: risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.
>
> Hi all,
>
> To follow up on Neil's email, the 1009 cases he mentions are those where we know from the antenatal consent data that the mother was approached for consent but consent was not obtained. Babies of those mothers were not necessarily born in the 24-27 week GA window, and we do not necessarily have GDB data for them. However, in the group of eligible but non-enrolled infants that were the comparison group for the most recent antenatal consent paper, there are 702 infants whose parents refused consent for SUPPORT. This is the group I would suggest using if you wanted to compare SUPPORT infants to those whose parents refused consent. The group whose parents refused consent might be more similar to the enrolled infants in that there was time for the consent process to take place, but there still could be some differences (perhaps in terms of maternal education or other characteristics).
>
> The factors we controlled for in the previous models to predict outcomes were gestational age, birth weight, sex, race, center, and antenatal steroid exposure.
>
> Marie
>
> Marie Gantz, Ph.D.

> Senior Research Statistician
> RTI International
> mgantz@rti.org
> 919-597-5110
>
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Tuesday, April 23, 2013 9:28 AM
> To: Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; Das, Abhik; Gantz, Marie; Wallace, Dennis; michele.walsh@UHhospitals.org
> Cc: Rich, Wade
> Subject: Re: risk adjusted mortality in the low sat group relative to that in nonenrolled eligible babies.
>
>
> Hello Everyone
>
> We have been looking at the SUPPORT Data regarding the Consent trial The data that we have for that study began after the first 6 months when the Consent study actually started. We had 2228 Moms who where approached,
> 1219 gave consent and 581 of the Mothers delivered within the window of the trial and thus accounted for 659 infants who where born and 611 who where enrolled in the trial. Remember that the consent trial only continued in each center until 50 infants delivered in the study window at that center.
> Remember that we only have data for women approached who then refused consent for the duration of the Consent Trial, which only accounted for slightly less than 1/2 of our overall enrollment. In addition this group is labelled as "Consent Not Obtained" which could mean that they did not actually have a consent presented or if they did there was no record of their response.
> Thus is you want to use only approached woman who refused consent, and use that number as your non-study group - it would include 1009 women and the corresponding number of infants they delivered.
> Thus we would no longer have a comparative group of 3053 eligible, whether approached or not.
> So as I understand the data, you would be comparing the outcomes of these approximately 1009 (probably more in view of multiples), with the actual study groups i.e. High SpO2, Low SpO2 CPAP , Surf if we did a full analysis.
>
> I prefer comparing all the eligibles as they represent infants who could have been enrolled under waiver and they represent all the available infants What do you want to do?
> I want to try to get a reasonable document together.
> We can use just the 1009 and see what the data shows - I would prefer to do both analyses - The approached and Non-consented as one control group and all eligibles as the other control group, versus the actual study groups in SUPPORT Please let me know if I have missed something (Probably so!!) I do not believe that we collected data for all the approached Mothers and whether they refused consent for the entire duration of the study as the screening log listed Moms who we believed would be eligible for the trial, and did not specify whether they where approached outside of the Consent Trial Window duration.
> The Consent Trial was started because we did not have such data and thought we needed it I will look forward to hearing from you.
> Regards
> Neil
>
> On 4/23/13 4:41 AM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu> wrote:
>
>> Marie's analytic plan may be all that is needed scientifically, and
>> approval by the subcommittee the most that would be needed to meet the
>> usual Network requirements for a secondary analysis. As previously
>> noted, the analyses proposed would appear to be no more a departure
>> from the original protocol than were the analyses already done and
>> would have been well justified at that time. The analyses I suggested
>> would add only a single predictor variable (center) to those previously
>> used (GA, birth weight, gender, race, center, and antenatal steroid exposure).
>>

>> While a better set of predictor variables might theoretically be
>> possible, we are less likely to be criticized for post hoc selection of
>> the model most to our advantage if we use the same predictors except
>> for adding center, and do not change the population. As I understand
>> Wally's position, any residual confounding is less likely if the
>> nonstudy babies were restricted to those eligible and parent(s) approached but refused.
>> Not having been involved in the discussions of the subcommittee, I am
>> not sure but such analyses would seem like a good idea consider.
>>
>>
>>
>> _____
>> From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
>> Sent: Tuesday, April 23, 2013 5:09 AM
>> To: 'nfiner@ucsd.edu'; Tyson, Jon E; 'wcarlo@peds.uab.edu';
>> 'adas@rti.org'; 'mgantz@rti.org'
>> Cc: 'wrich@ucsd.edu'
>> Subject: Re: risk adjusted mortality in the low sat group relative to
>> that in nonenrolled eligible babies.
>>
>> Neil
>> I did not see the proposal - please resend the document
>>
>> Thanks
>> Rose
>> Rosemary D. Higgins
>> Program Scientist for the NICHD Neonatal Research Network
>>
>> ----- Original Message -----
>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>> Sent: Tuesday, April 23, 2013 03:14 AM
>> To: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>; Wally Carlo
>> <wcarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das
>> <adas@rti.org>; Marie Gantz <mgantz@rti.org>
>> Cc: Rich, Wade <wrich@ucsd.edu>
>> Subject: Re: risk adjusted mortality in the low sat group relative to
>> that in nonenrolled eligible babies.
>>
>> Hi Jon
>> Sorry for any delay here
>> I am in Denmark and thus 6 hours ahead of you I agree that we need this
>> analysis- Now we have discussed it and the rationale for the data and
>> the fact that we have already defended our actions, I believe we now
>> need the actual analyses as additional relevant information The
>> Proposals for the analyses where put forward by me and Wade last week
>> we asked that this be done after there was agreement as to how to
>> proceed I will propose on todays call.
>> This is important since others John Lantos has used the analyses you
>> mention in his discussion in the Hastings Tweet " The babies in the
>> ³low oxygen² arm of the clinical trial
>>
>> had a mortality rate of 19.9%. The babies in the ³high oxygen² arm of
>> the study had a mortality rate of 16.2%. Babies in the
>>
>> network overall had a mortality rate of 24%. For severe retinopathy,
>> the numbers are 8.6% (low oxygen group), 17.9% (high
>>

>> oxygen group) and 24.1% (overall group). In other words, babies in both
>> arms of the study had higher survival rates and
>>
>> lower rates of retinopathy than babies who were not in the study. The
>> fact that some babies in the study were in the overall
>>
>> group minimizes these differences. The true differences were probably
>> larger. Babies enrolled in the study were protected,
>>
>> not endangered, by being in the study.
>>
>>
>> I would prefer that we do the proper analyses comparing the treatment
>> arms with infants simultaneously cared for in the NRN.
>>
>> I am copying Rose, Wally Abhik and Marie on this and hopefully the
>> group on the call can vote to move this ahead
>>
>> If this needs a SUPPORT Subcommittee member to take the lead, then I
>> will do that.
>>
>> Thanks for your continuing actions to provide the best evidence that
>> our actions in doing this trial where appropriate and based on the best
>> available evidence and the highest ethical principles
>>
>> Let me know if you want to talk further
>>
>> Be well
>>
>> Neil
>>
>>
>>
>> From: <Tyson>, Jon Tyson
>> <Jon.E.Tyson@uth.tmc.edu<mailto:Jon.E.Tyson@uth.tmc.edu>>
>> Date: Monday, April 22, 2013 3:28 PM
>> To: Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
>> Subject: risk adjusted mortality in the low sat group relative to that
>> in nonenrolled eligible babies.
>>
>>
>> Neil, would you please call me to discuss the following (office 713 500
>> 5651; cell (b)(6)
>>
>> I don't think the subcommittee has thought through the issue proposed
>> carefully enough and would propose to discuss by phone if you will call
>> a subcommittee call. I am only talking about adding an additional
>> predictor variable (treatment group) to the 6 used in the previously
>> conducted analysis described in the 2nd Wade paper ([3]Logistic
>> regression models were created to test the [3]trial effect[2] of enrollment
>> in SUPPORT on outcomes, controlling for GA, birth weight, gender, race,
>> center, and antenatal steroid exposure .[2]), This shouldn't require a
>> separate protocol to complement analyses that RTI did that weren't
>> included in Wade's original protocol but were done without a separate protocol.
>> Indeed, for reasons noted below, the proposed analyses arguably should
>> have been done before publishing the paper [3]Enrollment of Extremely
>> Low Birth Weight Infants in a Clinical Research Study May Not Be

>> Representative.[2] I believe we need to know the results of these
>> analyses and that they could well help us to deal with the issue that I
>> think is most important to the public which thinks that babies
>> randomized to the low sat arm were treated in a way that increased
>> their mortality relative to what it would have been done if they hadn't
>> participated in the trial.
>>
>> Abhik, wouldn't the original analysis of whether participation in the
>> trial affected mortality be meaningful only if there was an evaluation
>> of whether treatment group affected risk-adjusted mortality relative to
>> usual care? Suppose for example that it had turned out that risk of
>> death was say uniformly decreased by an absolute 20% in the high
>> saturation group relative to the usual care group and that risk of
>> death was uniformly increased by 20% in the low saturation group. It
>> would not be meaningful to say that risk was not increased by
>> participation in the trial because the overall mortality was the same
>> among all trial babies as in the usual care group. The effect of
>> participation in the trial would depend on what group the infant was
>> assigned to (in the same way that it would not be meaningful to
>> conclude there is no main treatment effect without assessing
>> interactions by treatment group to determine if the lack of an overall
>> difference reflected major effects in opposite directions in different subgroups).
>>
>>
>>
>> So, the analysis by treatment group might well already have been done
>> in conducting the analyses, or if wasn't done, arguably should have
>> been done to determine whether it was meaningful to conclude that
>> participation in the trial had no effect. If it wasn't done, why not
>> activate the usual process to getting it done. Even in the worst case
>> scenario, the low saturation group were found to have worse
>> risk-adjusted outcomes than the usual care non-enrolled patients [which
>> looks quite doubtful], we need to know that and couldn't have anticipated it.
>>
>>
>>
>> And if we use the same risk variables to adjust as already used, we
>> aren't susceptible to the criticism that we rigged the results. It
>> seems to be the only reason not to do this is if there is concern that
>> the original model was not well selected.
>>
>>
>>
>> Jon E. Tyson, MD, MPH
>> Michelle Bain Distinguished Professor
>> Director, Center for Clinical Research and Evidence-Based Medicine Vice
>> Dean for Clinical Research and Healthcare Quality
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>> Jon.E.Tyson@uth.tmc<mailto:Jon.E.Tyson@uth.tmc>.
>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: SUPPORT vs COT
Date: Wednesday, April 24, 2013 9:14:00 AM

Yes,
The name was changed prior to the start of the trial – late 2004 or early 2005- do you need an exact date? I would have to check with the coordinating center

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, April 24, 2013 7:32 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]
Subject: SUPPORT vs COT

Dear Rose,
Was the SUPPORT trial called the "CPAP and Oxygenation Trial (COT)" in 2004 when it was getting started?
When did the name change?

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Bock, Robert (NIH/NICHD) [E]
Cc: Rowe, Mona (NIH/NICHD) [E]
Subject: SUPPORT PAS abstract presentations
Date: Wednesday, April 24, 2013 9:08:00 AM
Attachments: LeVan, Changes in Therapy, 2013-04-16.pptx
Stevens, Breathing Outcomes, 2013-04-15.pptx
Vaucher, Antenatal Enrollment - Is Neurodevelopmental Outcome Representative, 2013-04-11.pptx

---

Bob

The Stevens one is a platform (10 min presentation, 5 min for questions). The other two are poster presentations – the authors stands by the poster for 2-3 hours and fields questions.

Rose

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CHANGES IN THERAPY AND OUTCOMES ASSOCIATED WITH THE SUPPORT TRIAL

Jaclyn M LeVan, DO; Luc P Brion, MD; Lisa A Wrage, MPH; for the NICHD Neonatal Research Network

In the NICHD Neonatal Research Network (NRN) SUPPORT Trial preterm neonates 24 weeks 0 days to 27 weeks 6 days gestational age (GA) were randomized to: (1) continuous positive airway pressure initiated in the delivery room (DR) and subsequent limited ventilation strategy or DR intubation with early surfactant administration; and (2) oxygen (O_2) saturation targets of 85-89% or 91-95%.
The interventions did not affect the primary outcomes, death or bronchopulmonary dysplasia (BPD) (O_2 use at 36 weeks, with an attempt at withdrawal of supplemental O_2 in those who were receiving < 30% O_2), and death or severe retinopathy of prematurity (ROP). However, randomization to low O_2 saturation targets increased deaths and decreased severe ROP.
We hypothesized that the percentage for DR intubation would decrease after dissemination of the results, and that BPD/death and severe ROP/death would not be affected.

- To compare DR intubation, BPD/death at 36 weeks, and severe ROP/death by discharge in time periods before SUPPORT and after publication of results
- To determine the potential impact of the results of the SUPPORT trial on clinical practice, specifically the percentage of endotracheal intubation in the DR in preterm inborn infants

- Retrospective cohort study using the prospective NRN generic database.
- Inclusion criteria: infants 24 weeks 0 days to 27 weeks 6 days GA born before (1/03-12/04) and after SUPPORT (1/10-12/12) at 11 centers which participated in SUPPORT and were part of NRN in 2003-12.
- Exclusion criteria: infants with syndromes/major malformations and those receiving comfort care.
- Primary outcome variables: DR intubation, composite of death or BPD at 36 weeks (oxygen use at 36 weeks of postmenstrual age), and composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital.
- Secondary outcome variables: Death at 36 weeks, BPD, severe ROP, death or mechanical ventilation at day of life 7, ventilator days among survivors
- Statistics: (1) Chi-square tests, Student t-tests, Wilcoxon tests;
(2) Robust Poisson regression models to obtain adjusted relative risks and 95% confidence intervals (CI) for primary outcomes; General linear models for continuous outcomes, results expressed as difference in means and 95% CI;
(3) Stratified chi-square test to assess whether the pre vs. post-SUPPORT proportion of DR intubations was significantly different in the combined group of centers with pre-SUPPORT DR intubations ≥ 80% and in the combined group of centers with pre-SUPPORT DR intubations < 80%.

- Total study population of 3,849 infants included in the study: 1,617 infants in the pre-SUPPORT group and 2,232 in the post-SUPPORT group.
- Baseline characteristics: There was more antenatal steroid use, maternal hypertension, and maternal diabetes in the Post-SUPPORT group (p value <0.0001).
- Primary outcomes: After adjustment the RR (post vs. pre-SUPPORT) for all primary outcomes was significantly < 1.00.
- Secondary outcomes: The adjusted RR (post- vs. pre-SUPPORT) for severe ROP, death or mechanical ventilation at day of life 7, were significantly < 1. In contrast, the RR for death at 36 weeks and for BPD were not significantly different from 1. Ventilator days among survivors decreased after SUPPORT.
- The proportion of DR intubations in the combined group of centers with pre-SUPPORT DR intubation ≥ 80% significantly decreased post-SUPPORT (90.2% vs. 75.1%, p<.0001) whereas in the combined group of centers with pre-SUPPORT DR intubations < 80% it did not (56.6% vs. 54.3%, p=0.46).

Table 1. Maternal and Neonatal Characteristics

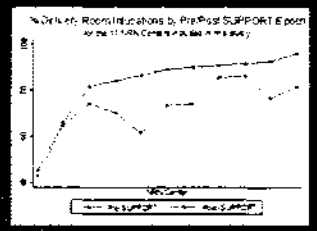
Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	P-Value
Birth Weight (g)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Males	858 (53.1)	1126 (50.5)	0.11
Antenatal Steroids	1338/1616 (82.8)	1994/2225 (89.6)	<0.0001
Maternal Hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal Diabetes	42 (2.6)	120/2231 (5.4)	<0.0001

Table 2. Primary Outcomes[&]

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	Adjusted RR 95% CI	Adjusted P-Value
Intubated in DR	1313 (81.2)	1539 (69)	0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.94 (0.89-0.99)	0.024
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	0.81 (0.73-0.89)	<0.0001
Death by discharge	358/1614 (22.2)	393/2196 (17.9)	0.86 (0.76-0.98)	0.02

Table 3. Secondary Outcomes

Outcome	Pre-SUPPORT N 1617	Post-SUPPORT N=1943	Adjusted RR or difference in means #	P-Value
BPD*	664/1311 (50.7)	855/1869 (45.8)	1.04 (0.97-1.1)	0.26
Death at 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.88 (0.76-1.00)	0.059
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.63 (0.52-0.77)	<0.0001
Days on Ventilator (survivors)**	22.3 (24.4), 13	17.8 (21.3), 9	-4.65 (-6.1,-3.2)	<0.0001
Death or Mechanical Ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	0.90 (0.84-0.97)	0.0033



- Infants 24 weeks 0 days to 27 weeks 6 days GA born at Network Centers after release of the results of SUPPORT had significantly decreased percentages of DR intubation, BPD or death, and ROP or death compared to those infants born before the initiation of SUPPORT at the 11 NRN centers participating in the trial.

- After adjustment for baseline variables, the relative risks (RR) (post- vs. pre-SUPPORT) of DR intubation, ROP/death, BPD/death and death to discharge, were significantly lower than 1.

- The adjusted RR (post- vs. pres-SUPPORT) for severe ROP and for death or mechanical ventilation at day of life 7 were significantly lower than 1. In contrast, the RR for death at 36 weeks and for BPD were not significantly different from 1. Ventilator days among survivors decreased after SUPPORT.

- These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites.

- More broadly, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this poster have been resolved. This poster does not involve discussion of unapproved or off-label, experimental or investigational use of a drug.

Acknowledgements: The National Institutes of Health: The Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in this study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University, Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California - San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University

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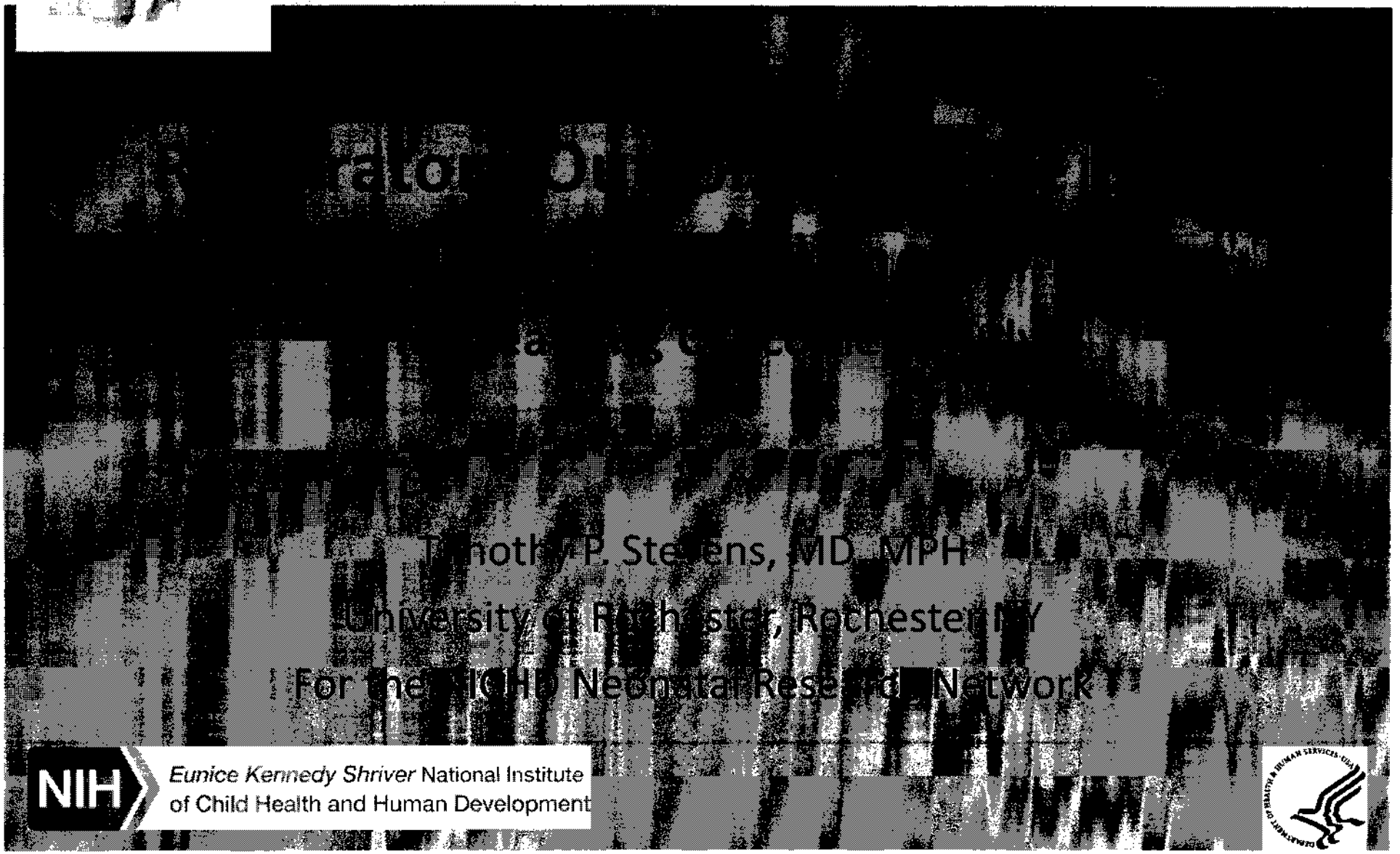
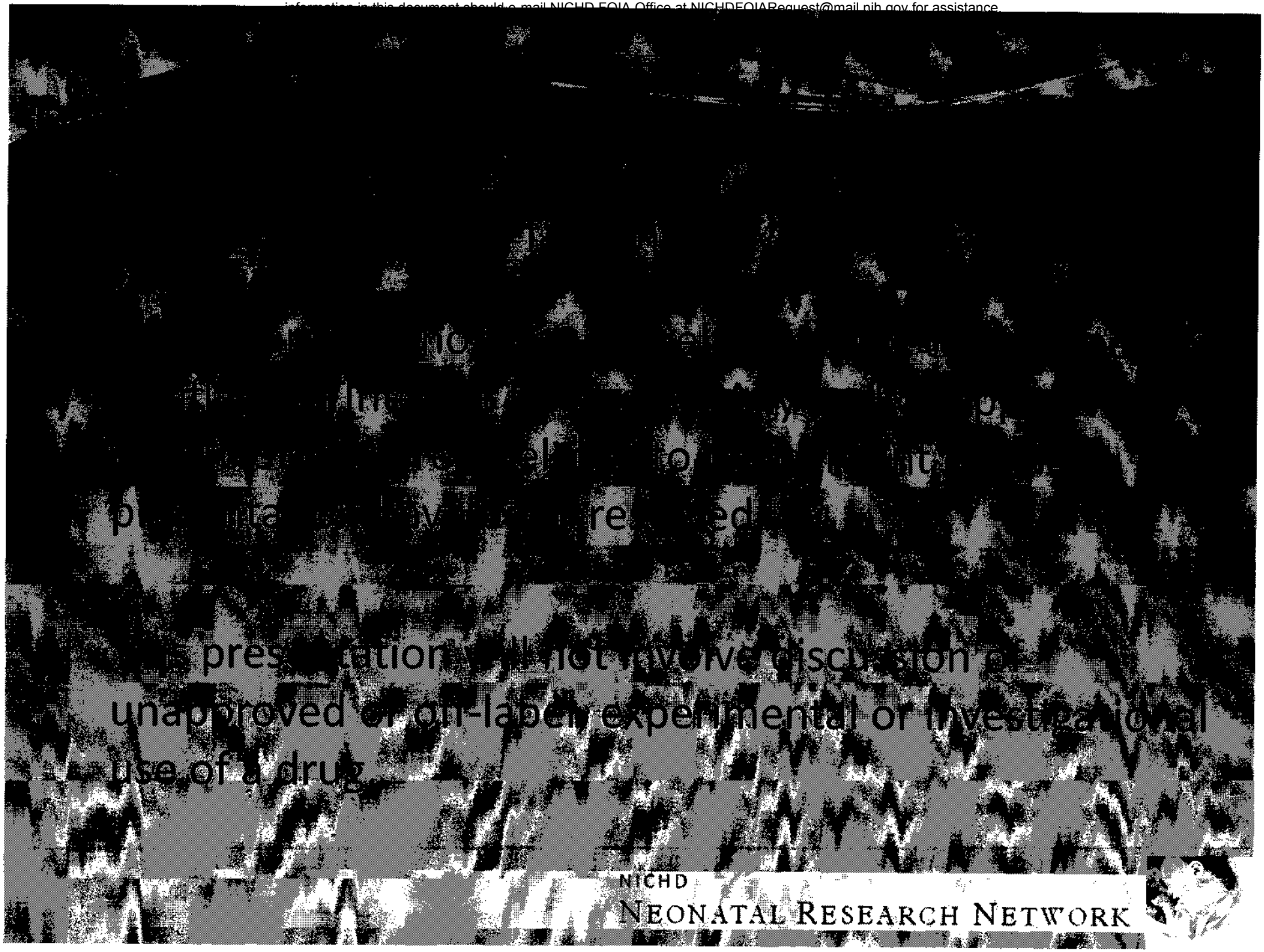


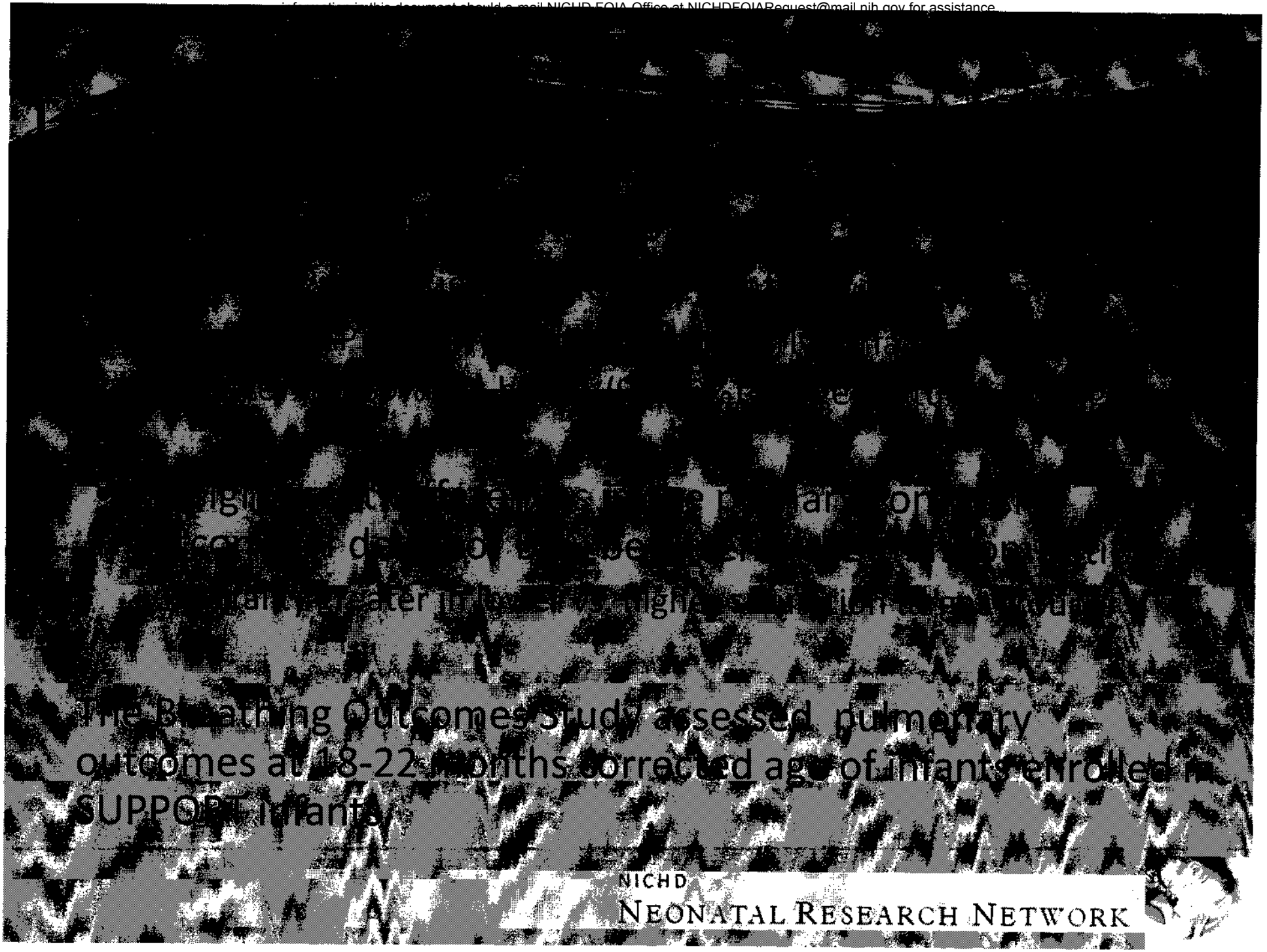
Timothy P. Stevens, MD, MPH

University of Rochester, Rochester NY

For the NICHD Neonatal Research Network

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development





The Breathing Outcomes Study assessed pulmonary outcomes at 18-22 months corrected age of infants enrolled in SUPPORT infants.

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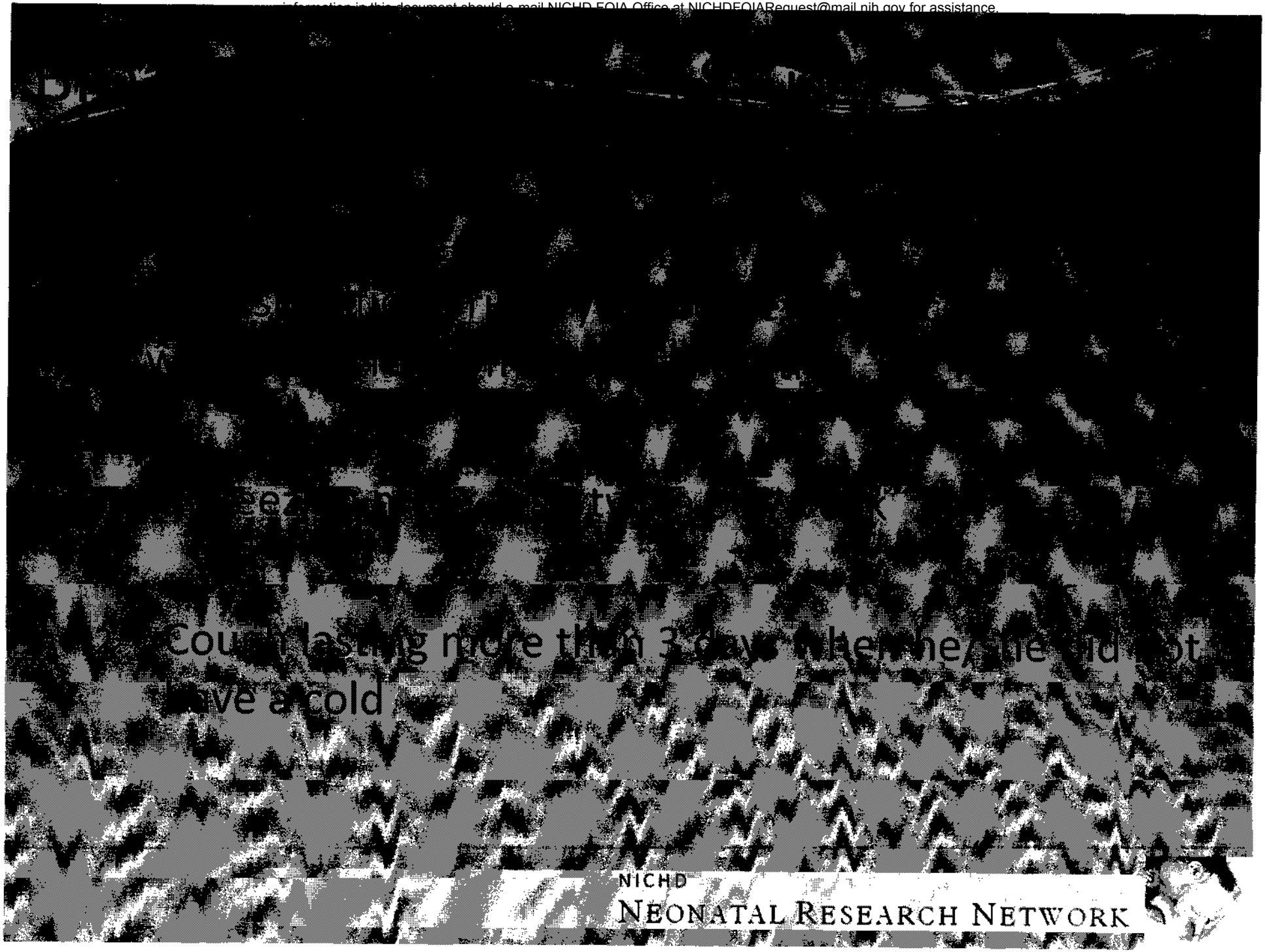

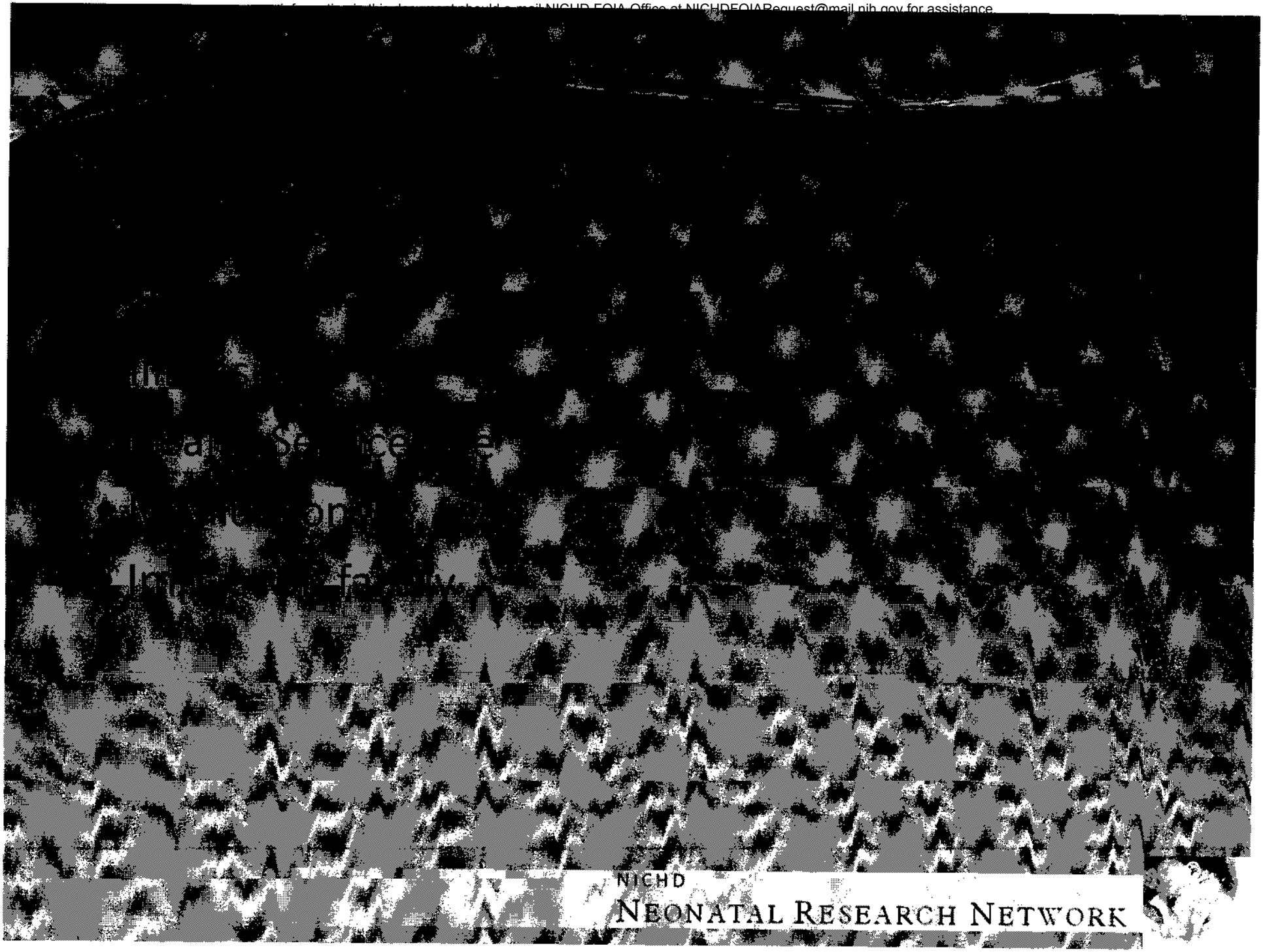

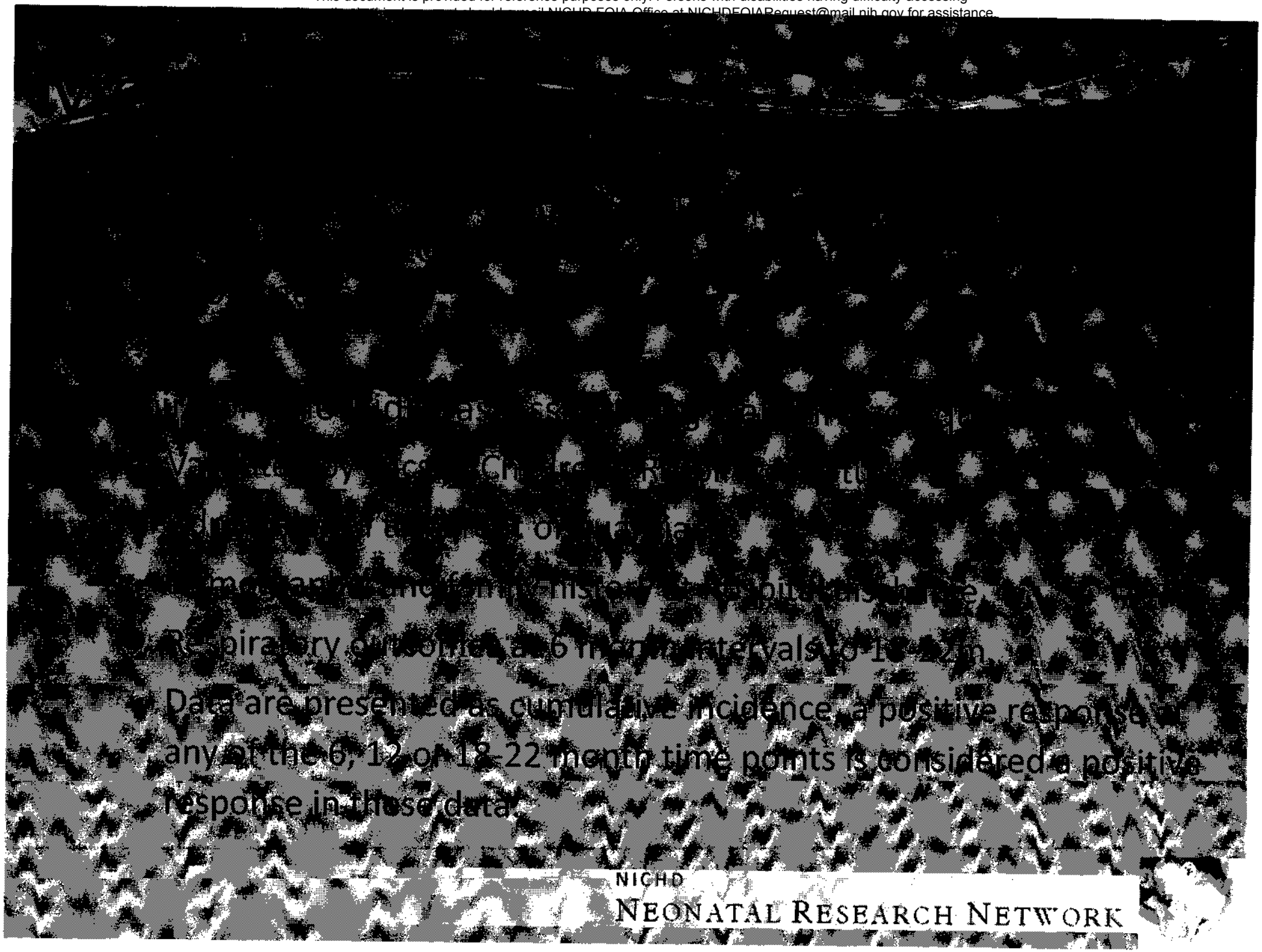

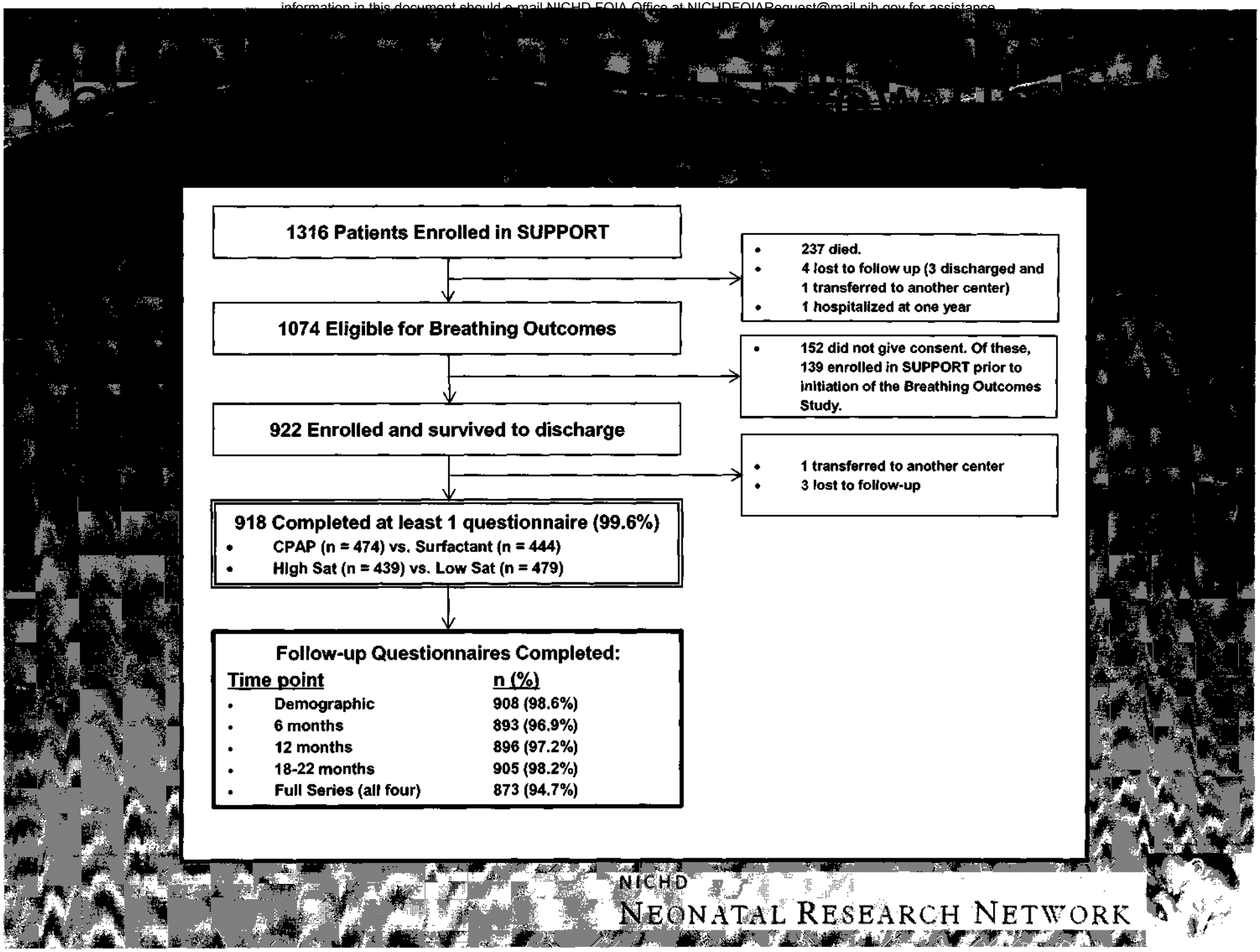

Characteristic - % unless noted	Low Sat N=439	High Sat N=479	CPAP N=474	Surfactant N=444
Birth Weight (g, mean ± s.d.)	858 ± 186	844 ± 190	850 ± 184	851 ± 193
Gestational Age (w, mean ± s.d.)	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0	25.9 ± 1.0
Male	50	54	49	55
Non-Hispanic White	39*	46*	40	46
NICU Hospitalization (d, median)	90	93	91	93
BPD (supplemental O2)	36*	46*	39	44
BPD (physiologic definition)	37	40	38	39.2
Discharged home				
On oxygen	24	23	23	24
On respiratory medications	27	27	28	27
October - March	53	48	49	51

*p<0.05

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Variable – %	Low Sat	High Sat	CPAP	Surfactant
	N=439	N=479	N=474	N=444
Family History of				
Asthma	32	32	31	33.0
COPD, emphysema	11	9	11	8.4
Food allergies	41	38	39	40
Chronic Respiratory Disease	2	1	0.2	3
Diet and Exposures				
Breast fed	37	30	34	33
Smoking in house	44	39	41	43
Spent time at daycare	42	33	38	36
Living with child under 12	61	62	60	63
Pets in home	41	36	39	38
Flu Shot	78	80	79	79
RSV Shot	72	73	73	72

Outcome n (%)	CPAP N=474	Surfactant N=444	ARR (95% CI)	p-value
Chest wheezy or whistling > 2x/wk?	224 (47.7)	212 (48.2)	0.90 (0.68, 1.19)	0.47
Cough >3d without a cold?	127 (28.4)	141 (33.7)	0.81 (0.60, 1.10)	0.18

Outcome n (%)	Low Sat N=439	High Sat N=479	ARR (95% CI)	p-value
Chest wheezy or whistling > 2x/wk?	203 (46.7)	233 (49.1)	0.92 (0.70, 1.22)	0.57
Cough >3d without a cold?	127 (30.8)	141 (31.1)	1.01 (0.75, 1.37)	0.93

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Outcome n (%)	CPAP	Surfactant	ARR (95% CI)	p-value
Wheezing/whistling >2x/w or cough >3d?	303 (67.8)	289 (68.7)	0.95 (0.70, 1.29)	0.74
Chest sounded wheezy or whistling?	269 (60.2)	262 (62.2)	0.86 (0.64, 1.15)	0.31
Chest wheezy or whistling apart from cold?	129 (28.9)	153 (36.5)	0.68 (0.50, 0.92)	0.01

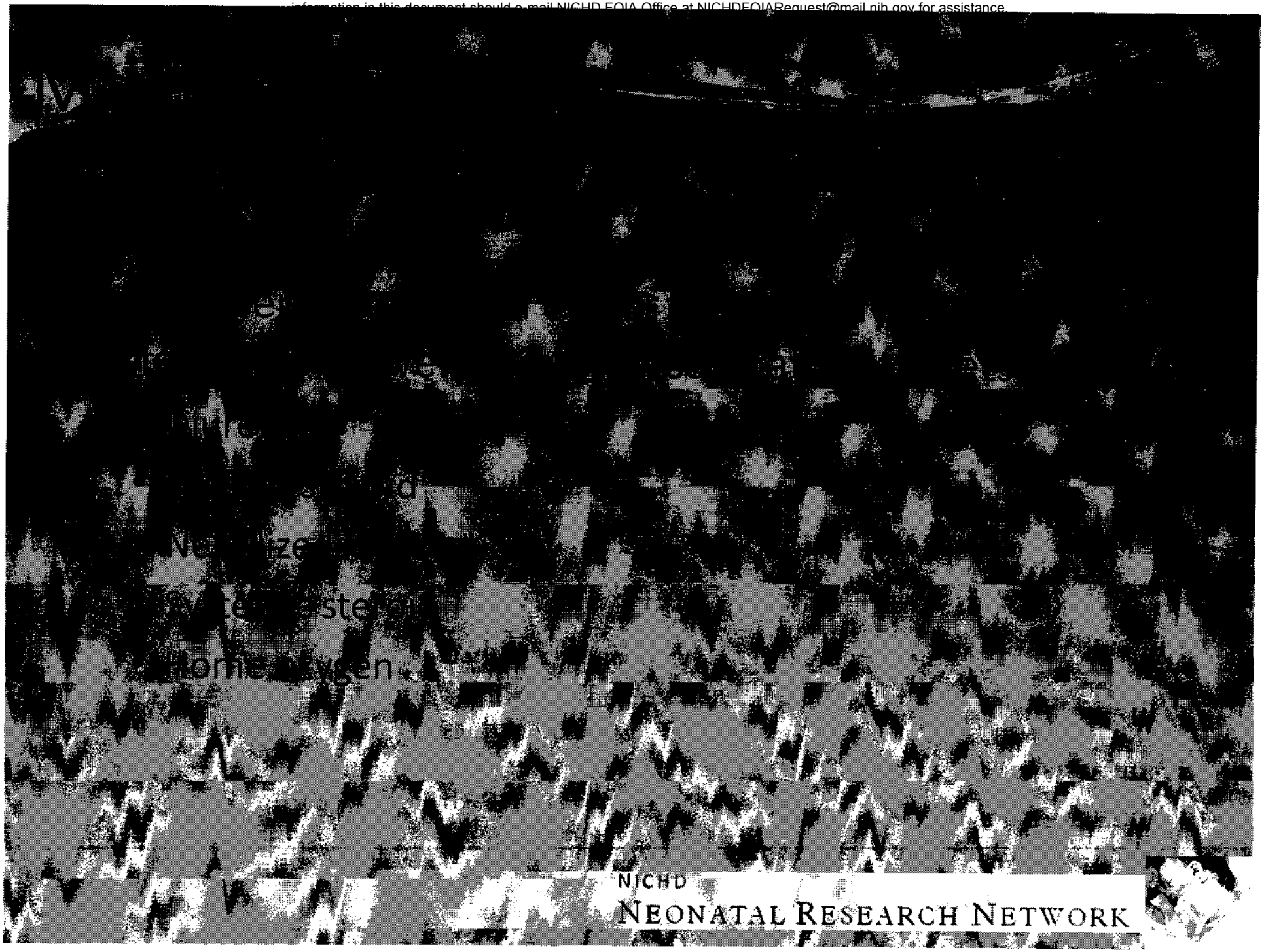
	Low Sat	High Sat	ARR (95% CI)	p-value
Wheezing/whistling >2x/w or cough >3d?	276 (66.8)	316 (69.5)	0.87 (0.65, 1.18)	0.37
Chest sounded wheezy or whistling?	245 (59.3)	286 (62.9)	0.85 (0.64, 1.13)	0.27
Chest wheezy or whistling apart from cold?	117 (28.4)	165 (36.3)	0.67 (0.49, 0.91)	0.01

Outcome n (%)	CPAP	Surfactant	ARR (95% CI)	p-value
Asthma, reactive airway disease, BPD flare?	144 (32.2)	154 (36.8)	0.81 (0.60, 1.09)	0.16
Bronchiolitis, bronchitis or pneumonia?	167 (37.4)	177 (42.2)	0.81 (0.61, 1.09)	0.17
Any of above?	213 (47.7)	232 (55.2)	0.71 (0.53, 0.95)	0.02

	Low Sat	High Sat	ARR (95% CI)	p-value
Asthma, reactive airway disease, BPD flare?	140 (33.9)	158 (35.0)	1.01 (0.75, 1.37)	0.93
Bronchiolitis, bronchitis or pneumonia?	161 (39.0)	183 (40.4)	0.96 (0.72, 1.28)	0.79
Any of above?	204 (49.4)	241 (53.1)	0.91 (0.69, 1.21)	0.52

Outcome n (%)	CPAP	Surfactant	ARR (95% CI)	p-value
Doctor or Emergency Room?	304 (68.0)	307 (72.9)	0.73 (0.53, 1.00)	<0.05
Hospital overnight for any reason?	181 (40.7)	186 (44.3)	0.87 (0.66, 1.16)	0.35
Hospital overnight for breathing problems?	130 (29.1)	139 (33.1)	0.82 (0.61, 1.11)	0.21

	Low Sat	High Sat	ARR (95% CI)	p-value
Doctor or Emergency Room?	292 (70.1)	319 (70.1)	0.98 (0.72, 1.34)	0.89
Hospital overnight for any reason?	169 (41.0)	199 (43.7)	0.90 (0.68, 1.20)	0.48
Hospital overnight for breathing problems?	129 (31.3)	141 (30.8)	1.04 (0.77, 1.40)	0.8



Outcome n (%)	CPAP	Surfactant	ARR (95% CI)	p-value
Change plans because of child's breathing?	145 (32.4)	164 (39.0)	0.74 (0.55, 1.00)	<0.05

	Low Sat	High Sat	ARR (95% CI)	p-value
Change plans because of child's breathing?	139 (33.7)	170 (37.4)	0.87 (0.65, 1.17)	0.36

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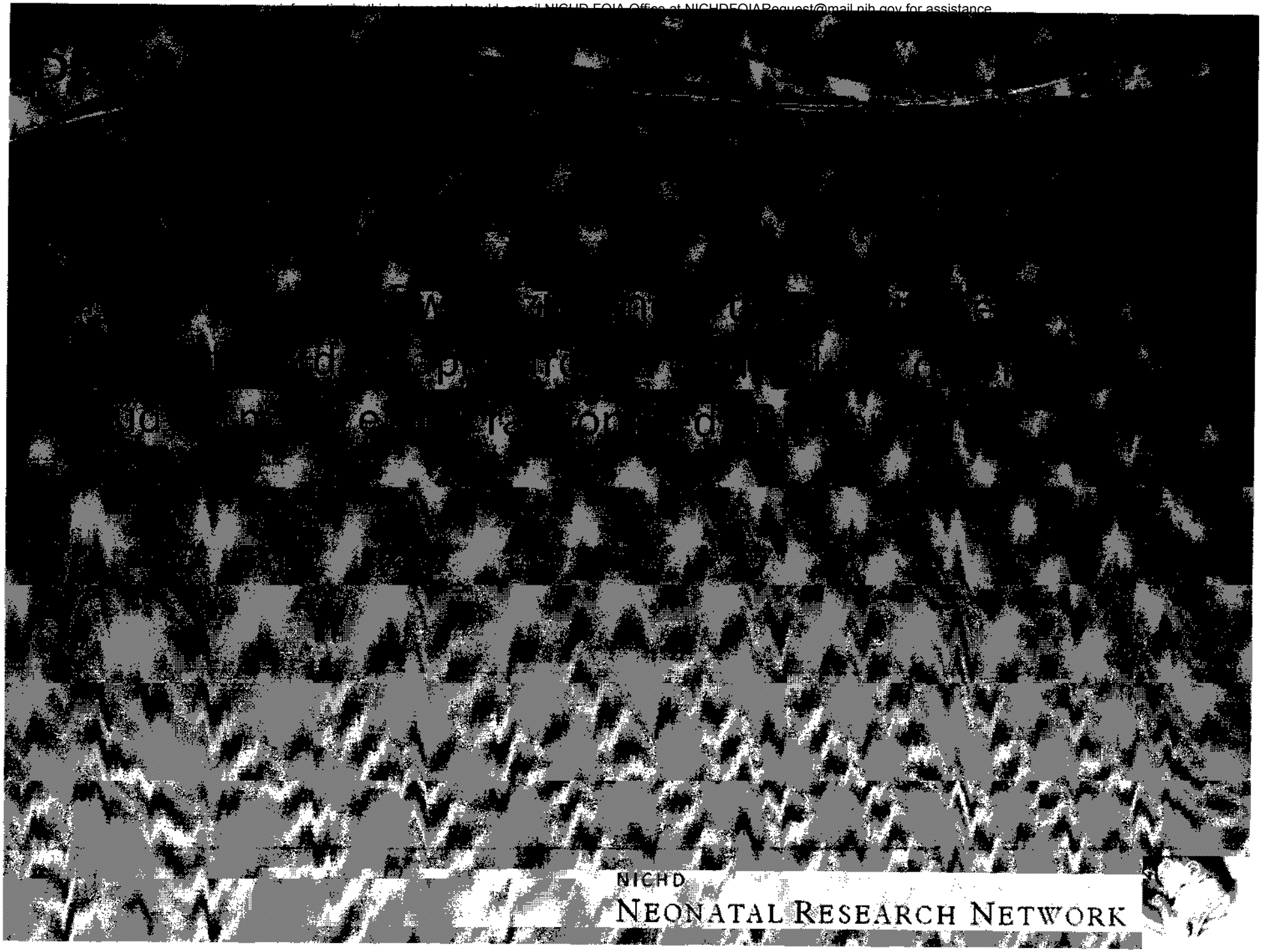

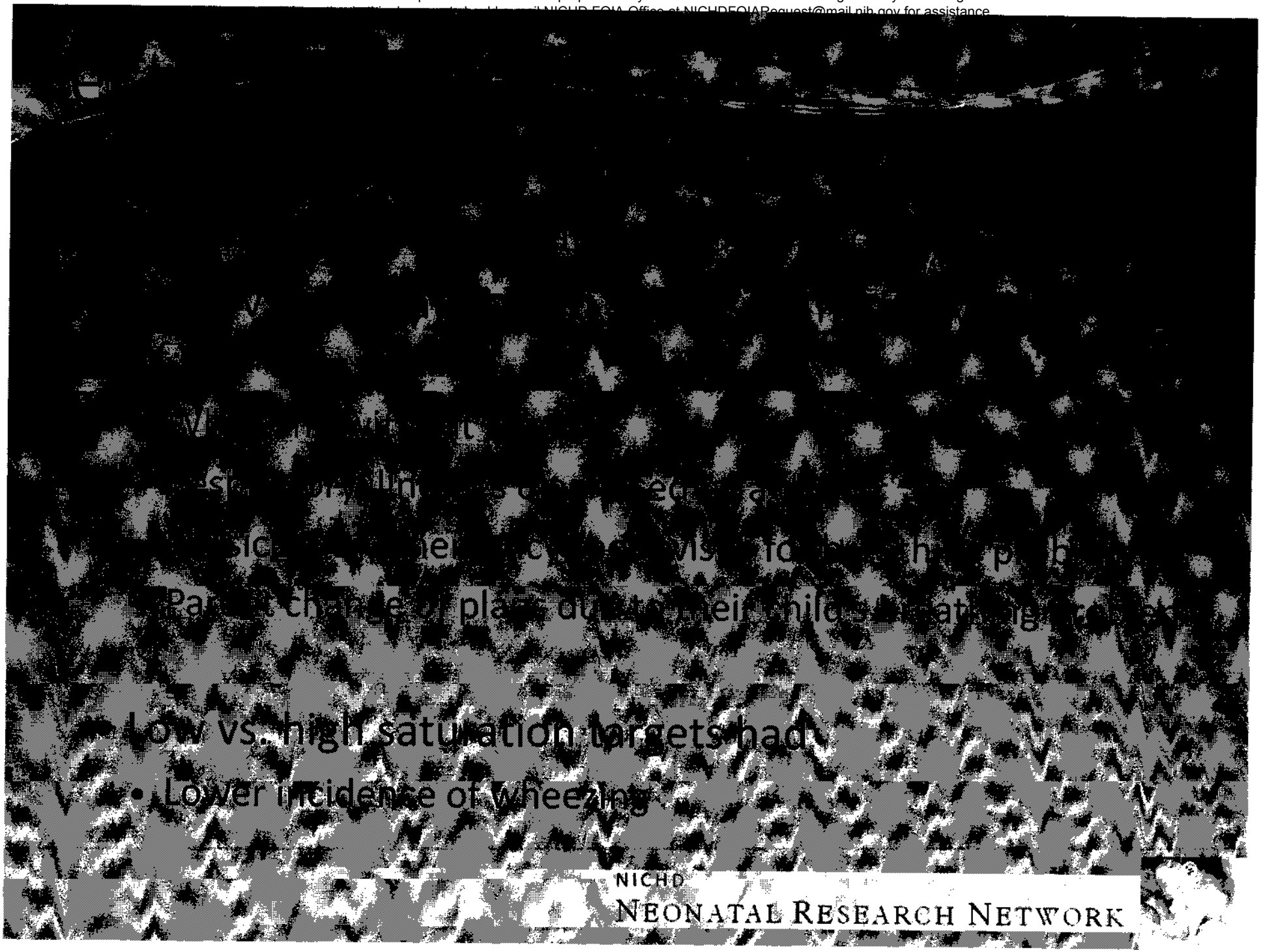

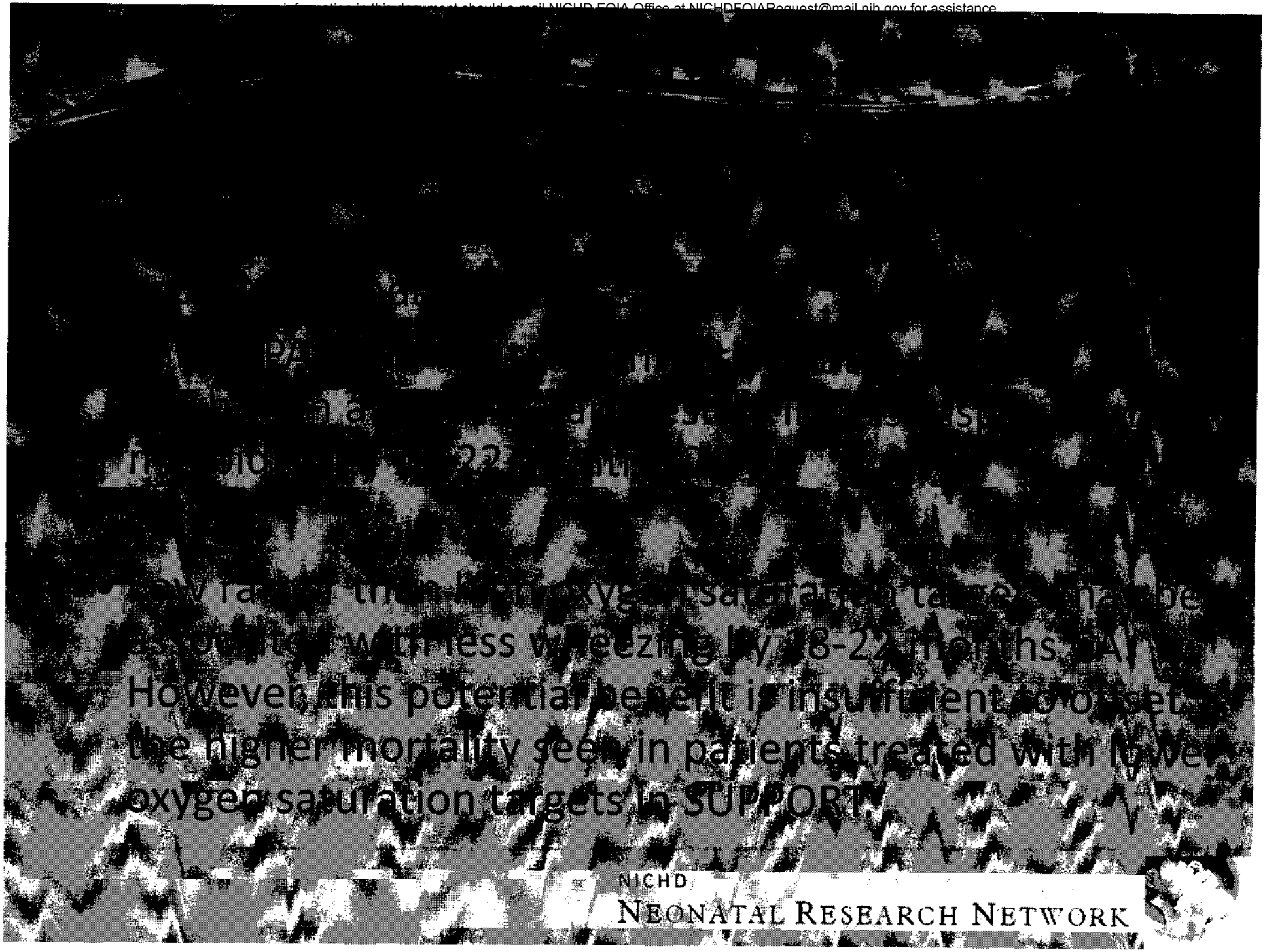

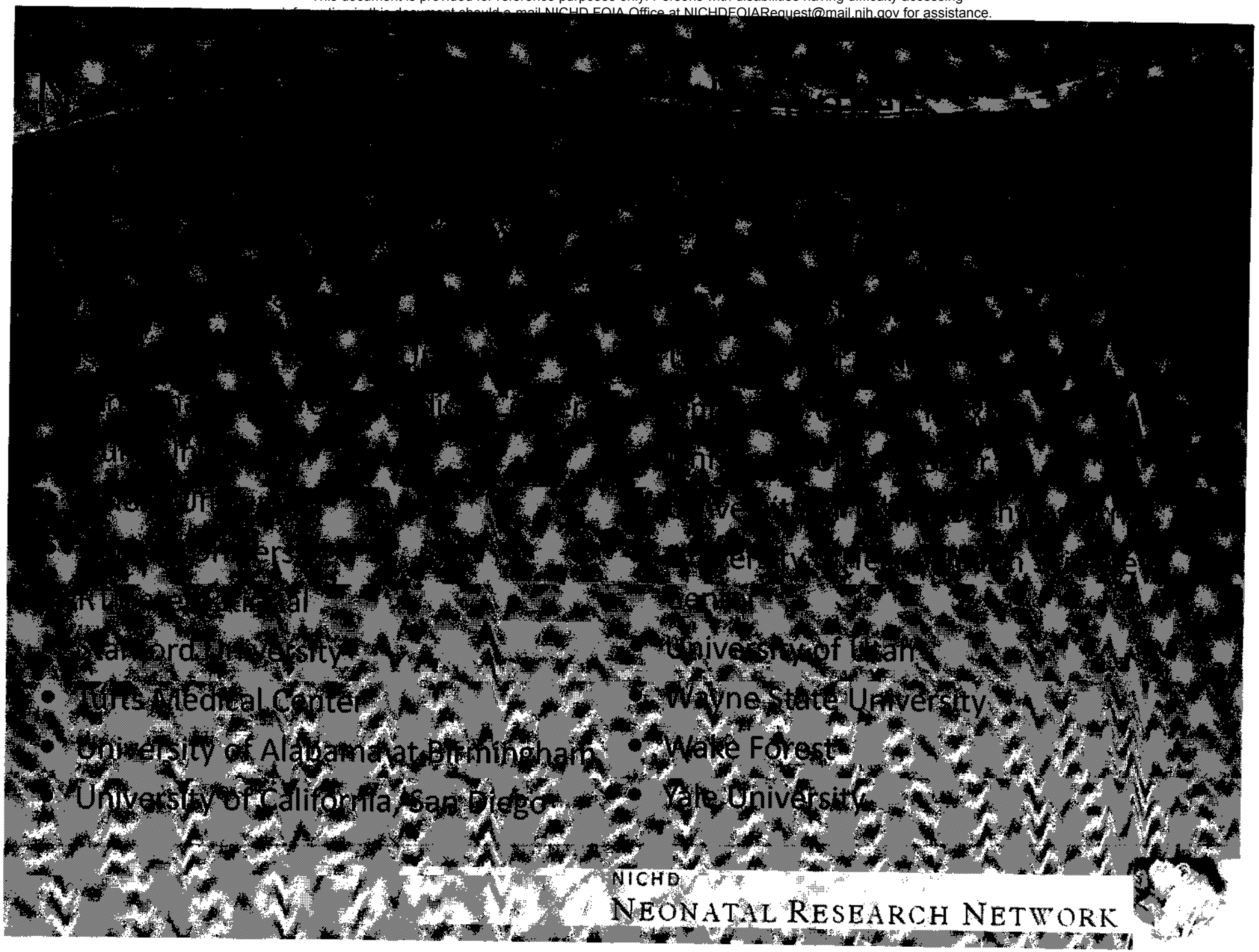

NICHD
NEONATAL RESEARCH NETWORK

Antenatal Enrollment in Clinical Trails: Is Neurodevelopmental Outcome Representative?

Yvonne E. Vaucher[1], Susan R. Hintz[2], Wade Rich[1], Marie G. Gantz[3] and Neil F. Finer[1] for the SUPPORT Subcommittee of the NICHD Neonatal Research Network
[1]University of California, San Diego, CA; [2]Stanford University, Palo Alto, CA; [3]RTI International, Research Triangle Park, NC

Antenatal enrollment in the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) was necessary in order to conduct the trial which included intervention immediately after delivery.

Antenatal enrollment was associated with differences in demographic, antenatal and neonatal characteristics between enrolled vs. eligible, non-enrolled preterm infants.

Mothers of eligible/non-enrolled infants were *less likely* to be white/non-Hispanic, insured, have had prenatal care (PNC) or receive antenatal steroids (ANS).[1]

Eligible/non-enrolled preterm infants were *more likely* to have lower gestational age (GA), lower birthweight (BW), and lower Apgar scores, require delivery room resuscitation, develop BPD and severe IVH and die before discharge.[2]

The primary, composite neurodevelopmental outcome of SUPPORT was death or neurodevelopmental impairment (NDI) at 18-22 months corrected age.

To determine whether antenatal enrollment in SUPPORT was associated with differences in Death and NDI in enrolled vs. eligible/not enrolled children.

We included all 24-26 week GA infants at Neonatal Research Network sites with birth weight > 400g, born from 1/2006 to 2/2009, who were eligible for SUPPORT. For surviving children a comprehensive neurodevelopmental evaluation was performed at 18-22 months corrected age (CA) using a standardized neuromotor assessment and the cognitive scale of the Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III).

Outcomes compared for the enrolled vs. eligible/non-enrolled children were Death or NDI and levels of cognitive delay. NDI was defined as having a BSID-III cognitive score <70, a Gross Motor Function Classification System Score (GMFCS) ≥2, moderate-severe cerebral palsy (CP), blindness or deafness.

Logistic regression models controlled for center, gender, race, GA, BW, insurance status, PNC, ANS, Apgar scores and DR resuscitation.

Death or NDI was determined for 95.3% (695/729) of children enrolled in SUPPORT vs. 90.9% (1471/1618) of the eligible/non-enrolled children (p <.001).

In unadjusted analyses eligible/non-enrolled children were more likely to have Death or NDI (41.4% vs. 33.4%, p<.001), to die before 18-22 months CA (31.7% vs. 24.8), p <.001), and to have cognitive scores <80 (19.9% vs. 15.5%, p<.038). There were no differences between the enrolled vs. eligible/non-enrolled in NDI (10.4 vs. 12.0%), GMFCS ≥ 2 (4.8 vs. 6.3%), moderate-severe CP (4.0 vs. 4.9 %), bilateral blindness (1.0 vs. 1.2%), deafness (3.1 vs. 2.3%), cognitive score < 70 (7.4 vs. 8.5%) or <85 (26.0 vs. 29.1%).

In adjusted models antenatal and neonatal risk factors predicted Death or NDI and BSID-III cognitive scores <80 while enrollment *did not* (Tables 1 and 2).

Table 1: Demographic, antenatal and Delivery Room Predictors of Death or NDI at 18-22 months CA

Center	--	<.0001
Enrolled in SUPPORT	0.94 (0.75, 1.16)	0.55
White, non-Hispanic	1 (0.81, 1.24)	0.99
At least one PNC visit	1.18(0.75, 1.84)	0.47
Antenatal steroids [any]	0.77(0.56,1.06)	0.11
Uninsured/self-pay	1.25(0.87, 1.78)	0.22
Gestational age at birth (weeks)	0.68 (0.56, 0.73)	<.0001
Birth weight (100 g)	0.77(0.71, 0.83)	<.0001
Male	1.8 (1.48, 2.19)	<.0001
Apgar at 5 minutes < 3	2.37(1.62,3.47)	<.0001
DR resuscitation: Chest compressions or epinephrine	1.33(0.95, 1.85)	0.10

Table 2. Predictors of BSID-III Cognitive score < 80 in survivors

Center	--	<.0001
Enrolled in SUPPORT	0.81(0.58, 1.13)	0.22
Gestational age (weeks)	0.91(0.73, 1.12)	0.36
Birth weight (100 g)	0.77 (0.68, 0.88)	<.0001
Male	1.79 (1.31, 2.43)	.0002
Antenatal steroids (any)	0.54(0.34,0.87)	.011
BPD	1.48(1.05-2.09)	.025
Severe IVH (Grades 3-4) or PVL	2.88(1.98-4.18)	<.0001
Severe ROP	2.25(1.54, 3.29)	<.0001

Compared to children enrolled in SUPPORT, those who were eligible but not enrolled were more likely to die, to have a composite outcome of death or NDI and to have lower cognitive scores. These differences are attributable to demographic, antenatal and neonatal differences that favored those who were enrolled in SUPPORT.

Rich W, et al. Antenatal Consent in the SUPPORT Trial: Challenges, Costs, and Representative Enrollment. *Pediatrics* 2010;126: e215-Oe221
Rich W, et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. *Pediatrics* 2012;129:1-5

Disclosures: The authors have no financial relationships to disclose or conflicts of interest to resolve. Any real or apparent conflicts of interest related to the content of this poster have been resolved. This poster does not involve discussion of unapproved or off label, experimental or investigational use of a drug.
Acknowledgements: The National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development provided grant support for the Neonatal Research Network. We are indebted to the infants and their parents who agreed to take part in the study and to our medical and nursing colleagues at: Brown University; Case Western Reserve University, Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; RTI International; Stanford University; Tufts Medical Center; University of Alabama at Birmingham; University of California - San Diego; University of Iowa; University of Miami; University of New Mexico; University of Rochester; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; University of Utah; Wake Forest University; Wayne State University; Yale University.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Gordon, Valery (NIH/OD) [E]
Subject: RE: About SUPPORT
Date: Tuesday, April 23, 2013 4:54:00 PM
Attachments: Poindexter, Glutamine, Pediatrics, 05-2004.pdf

Here is the glutamine paper – again we have no press release –
This is the final email – let me know if you need additional information.,

Regards
Rose

Rosemary D. Higgins, MD
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From: Gordon, Valery (NIH/OD) [E]
Sent: Tuesday, April 23, 2013 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: About SUPPORT

Thank you very much.

1. We want to write a paragraph that starts with: (b)(5)

   (b)(5)

   We asked for a couple of examples, but I think that the request was insufficiently clear. We need a couple (or 3) examples of (b)(5)

   (b)(5)

2. The next paragraph currently contains the following information: (b)(5)

   (b)(5)

I obtained this information from protocols, publications, editorials, and letters. But was there something significant about the 1950's? And what was meant by (b)(5) Does it mean (b)(5) Is there more (b)(5) And what happened after the 1950's? I found meta-analyses conducted between 2000 and 2009 (Cochrane Database Syst. Rev.). But surely something was done between 1950 and 2000?

These are the issues for which we need information at the moment.
If it is easier to talk with me on the phone, I provide my direct number below.

I appreciate your assistance with this project and your willingness to share your expertise.
Valery

Valery Gordon Ph.D., M.P.H.

Acting Director, Clinical Research Policy,

Office of Science Policy, OD

NIH

(301) 402-7667 (direct phone)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, April 23, 2013 2:16 PM
To: Gordon, Valery (NIH/OD) [E]
Subject: RE: About SUPPORT

That is fine.
Happy to try to answer any questions

Best regards
Rose

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From: Gordon, Valery (NIH/OD) [E]
Sent: Tuesday, April 23, 2013 2:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: About SUPPORT

Hello Rosemary,
I don't think we've met, but I am part of the OSP team that is drafting an editorial for the NIH Director. The editorial is about research with pre-term infants and uses the SUPPORT study as an example of valuable research that has informed the care of these infants.
We have been working through Mona Rowe, who has obtained information from you and then passed it back to us. I can continue to use this pathway if this is best, or if it would be OK, I wonder if I can ask you a few questions that will help us to complete a draft of this document.
Would you please let me know?
Thank you,
Valery

Valery Gordon Ph.D., M.P.H.

Acting Director, Clinical Research Policy,

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Parenteral Glutamine Supplementation Does Not Reduce the Risk of Mortality or Late-Onset Sepsis in Extremely Low Birth Weight Infants

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ABSTRACT. *Background.* **Glutamine is one of the most abundant amino acids in both plasma and human milk, yet it is not included in standard intravenous amino acid solutions. Previous studies have suggested that parenteral nutrition (PN) supplemented with glutamine may reduce sepsis and mortality in critically ill adults. Whether glutamine supplementation would provide a similar benefit to extremely low birth weight (ELBW) infants is not known.**

Methods. **We performed a multicenter, randomized, double-masked, clinical trial to assess the safety and efficacy of early PN supplemented with glutamine in decreasing the risk of death or late-onset sepsis in ELBW infants. Infants 401 to 1000 g were randomized within 72 hours of birth to receive either TrophAmine (control) or an isonitrogenous study amino acid solution with 20% glutamine whenever they received PN up to 120 days of age, death, or discharge from the hospital. The primary outcome was death or late-onset sepsis.**

Results. **Of the 721 infants who were assigned to glutamine supplementation, 370 (51%) died or developed late-onset sepsis, as compared with 343 of the 712 infants (48%) assigned to control (relative risk: 1.07; 95% confidence interval: 0.97–1.17). Glutamine had no effect on tolerance of enteral feeds, necrotizing enterocolitis, or growth. No significant adverse events were observed with glutamine supplementation.**

Conclusions. **Parenteral glutamine supplementation as studied did not decrease mortality or the incidence of late-onset sepsis in ELBW infants. Consequently, although no harm was demonstrated, routine use of parenteral glutamine supplementation cannot be recommended in this population.** *Pediatrics* **2004;113:1209–1215;** ***glutamine, parenteral nutrition, extremely low birth weight infants, randomized clinical trial.***

ABBREVIATIONS. PN, parenteral nutrition; ELBW, extremely low birth weight; RR, relative risk; CI, confidence interval.

Although glutamine is the most abundant amino acid in both plasma and human milk,[1] it is not included in standard intravenous amino acid solutions because of its limited stability in solution and the assumption that it is a nonessential amino acid. Previous studies in animals and critically ill adults have suggested that parenteral nutrition (PN) supplemented with glutamine reduces the risk of sepsis and mortality.[2,3] However, it is unclear whether parenteral glutamine supplementation would provide a similar benefit to premature infants.

We conducted a multicenter, randomized, double-masked clinical trial to determine the efficacy and safety of parenteral glutamine supplementation in extremely low birth weight (ELBW) infants (birth weight ≤ 1000 g). Our primary hypothesis was that parenteral glutamine supplementation would decrease the risk of death or late-onset sepsis.

METHODS

Study Infants

Inclusion criteria were a birth weight of 401 to 1000 g and the presence of intravenous access. To facilitate early initiation of PN, we enrolled all infants within 72 hours after birth. We excluded infants with major congenital anomalies, those with congenital nonbacterial infection, those thought to have a terminal illness (as indicated by a pH <6.80 or the presence of hypoxia with bradycardia for >2 hours), and those for whom a decision had been made not to provide full support. The study was conducted at 15 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network (see Appendix 1) between October 1999 and August 2001. The institutional re-

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Received for publication May 15, 2003; accepted Jul 23, 2003.
This work was presented in part at the Pediatric Academic Societies' Annual Meeting, Baltimore, MD, May 5, 2002.

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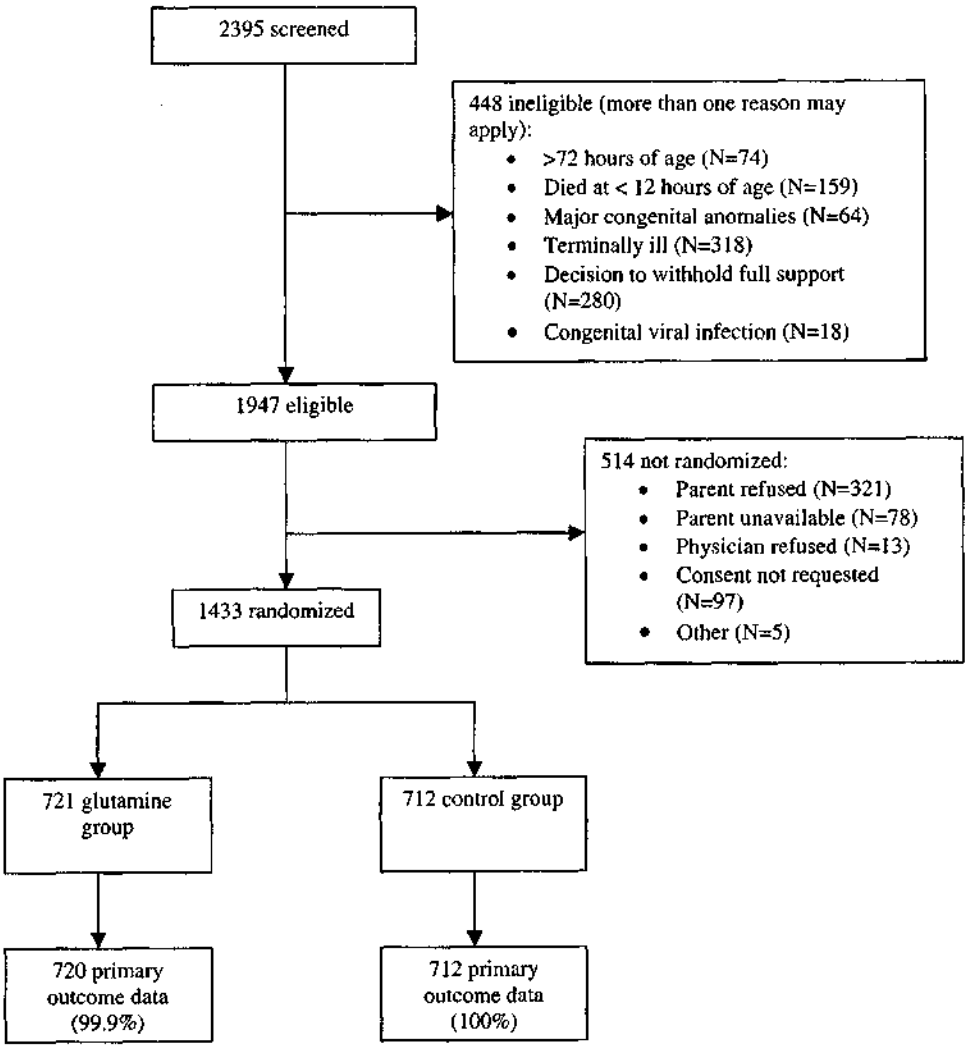

Fig. 1. ELBW infants (401–1000 g) screened and randomly assigned to the glutamine and standard PN groups.

view board at each center approved the study protocol, and written, informed consent was obtained from a parent of each infant.

Randomization

The infants were stratified by center and by birth weight (401–750 or 751–1000 g). The hospital pharmacist assigned the infants to the control or glutamine group by using a randomization list provided by the data-coordinating center (Research Triangle Institute).

Intervention

Infants in the control group received TrophAmine (B Braun, Irvine, CA) as their intravenous amino acid solution, and infants in the glutamine group received an isonitrogenous study amino acid solution with 20% glutamine, which consisted of TrophAmine and nonpyrogenic L-glutamine powder (Ajinomoto, Raleigh, NC). A US Food and Drug Administration-approved drug manufacturer compounded the study amino acid solution under controlled, clean-room conditions (Central Admixture Pharmacy Services, Inc, Irvine, CA). Before beginning the study, both Central Admixture Pharmacy Services and the laboratory at Indiana University School of Medicine documented sterility and stability of the glutamine-enriched amino acid solution to 17 weeks. The hospital pharmacist labeled all bags of PN with the final amino acid concentration. Research nurses recorded the volume of PN that the infant received on a daily basis, thereby permitting calculation of actual amino acid intake. The glutamine-enriched solution was visually indistinguishable from standard PN; consequently, caregivers were masked to the treatment group. A standard dose of cysteine hydrochloride (40 mg/g amino acid; 120 mg/kg per day maximum)[4,5] was added to the final compounded bag of PN in both groups.

Although the study protocol specified guidelines for the use of PN, including early initiation and rapid advancement of amino acid intake to 3 to 3.5 g/kg per day, the neonatologist caring for the infant determined the appropriateness of and final prescription for the total PN and made all decisions related to the introduction and advancement of enteral feeds. Infants received study PN and were followed until they were discharged from the hospital, died, or reached 120 days of age, whichever came first.

Outcomes

The primary outcome was the composite of death or late-onset sepsis (positive blood or cerebrospinal fluid culture for bacteria or fungi obtained after 72 hours of age in the presence of compatible clinical signs of septicemia). Secondary outcomes included the number of episodes of late-onset sepsis, incidence of proven necrotizing enterocolitis,[6] days on the ventilator, length of hospital stay, tolerance of enteral feeds (full enteral feeds were defined as receiving ≥110 kcal/kg per day enterally), feeding intolerance (defined by the need to hold enteral feeds ≥24 hours), total duration of PN, and growth. To monitor safety, we also recorded laboratory values from routine PN monitoring when obtained. In addition, plasma amino acid and ammonia concentrations were obtained and centrally analyzed in the first 10 infants enrolled at each center before initiation of study PN and again after receiving study PN for ~10 days.[7] Research nurses collected all study data using defined criteria and standardized study forms; all data were

subsequently transmitted electronically to the central data-coordinating center.

Statistical Analysis

The study was designed to identify a 20% relative reduction in mortality or late-onset sepsis with 80% power and a 2-tailed type I error of 0.05. Assuming a 35% incidence of death or late-onset sepsis among ≤1000-g birth weight infants,[8] we calculated that 690 infants per group would be required.

Data were analyzed by using SAS software (SAS Institute Inc, Cary, NC). The analysis of the differences in baseline characteristics used the Wilcoxon rank sum test for continuous variables and Fisher's exact or χ^2 tests for categorical variables. The 2 groups were compared according to the intention to treat. Primary outcome measures were adjusted for center and birth weight stratum.

An independent data monitoring committee used the Lan-DeMets procedure[9] with an O'Brien-Fleming spending function[10] to assess efficacy. Two interim analyses were performed at the predetermined intervals of 25% and 50% of targeted enrollment.

RESULTS

Study Infants and Intervention

The numbers of infants who were screened and randomized are shown in Fig 1. A total of 1433 infants were randomized; the baseline characteristics of the infants in the 2 groups were similar (Table 1). Timing and characteristics of PN administration are shown in Table 2. Parenteral amino acid intake over the first 14 days of the study and the day of life of first receipt of a minimum of 3 g/kg per day of intravenous amino acids were similar between the 2 groups.

Primary Outcome

Primary outcome data were available for 1432 of the 1433 infants enrolled in the trial (culture results were not available for 1 infant who was transferred to a non–network facility). Parenteral glutamine supplementation did not decrease the rate of mortality or late-onset sepsis. The primary outcome of death or late-onset sepsis occurred in 51% of infants in the glutamine group and in 48% of infants in the control group (relative risk [RR]: 1.07; 95% confidence interval [CI]: 0.97–1.17; $P = .18$) (Table 3). There was also no evidence that glutamine supplementation altered the rates of either death or late-onset sepsis. There was no difference between the study groups in the number of episodes of culture-proven sepsis. Adjusting for the antenatal administration of glucocorticoids yielded the same RR. In addition, logistic regression models for each primary outcome revealed that there was no statistically significant interaction between treatment effect and center.

Secondary Outcomes

Approximately 10% of the infants in each group developed necrotizing enterocolitis.[6] The need for surgical intervention was similar in both groups (Table 4). There was no difference between the groups in number of days on the ventilator or in the length of hospital stay. The number of days to first and full enteral feeding was also similar in the 2 groups (Table 5); however, infants in the glutamine group received PN an average of 2 days longer than those in the control group ($P = .05$). The incidence of feeding intolerance and the number of episodes of feeding intolerance was similar in both groups, as was the number of days to reach 1500 g and the weight at 36 weeks' postmenstrual age.

Safety of Glutamine Supplementation

Infants in the glutamine group had a higher maximal serum urea nitrogen than the infants in the control group; however, there was no difference in the number of infants with a serum urea nitrogen >40 mg/dL (Table 6). Plasma amino acid and ammonia concentrations were measured and have been reported previously in a subgroup of the first 141 infants enrolled in the trial.[7] In infants randomized to receive glutamine, mean plasma glutamine concentrations increased significantly and were 30% higher than in the control group after ~10 days of study PN (Table 6). There was no significant change in the mean plasma ammonia concentration between the baseline and study PN sample in the glutamine group.

DISCUSSION

This is the first large, randomized, double-masked, multicenter trial of parenteral glutamine in ELBW infants. Previous data in critically ill adults and animal models suggest that glutamine may have an important role in reducing the risk of death and infection by enhancing immune function and gut integrity. Thus, glutamine supplementation is an at-

TABLE 1. Baseline Characteristics of ELBW Infants Randomized to a Parenteral Glutamine Trial

Characteristic	Glutamine Group (n = 721)	Control Group (n = 712)
Birth weight, g	770 ± 141	768 ± 138
Gestational age, wk	26.0 ± 2.1	25.9 ± 1.9
Small for gestational age*, n (%)	121 (17)	110 (15)
Race or ethnic group, n (%)		
Black	350 (49)	309 (43)
White	256 (36)	278 (39)
Hispanic	103 (14)	112 (16)
Other	12 (2)	13 (2)
Male, n (%)	340 (47)	344 (48)
Antenatal glucocorticoid therapy, n (%)	585 (81)	548 (77)
Apgar score ≤3, n/total n (%)		
At 1 min	253/713 (35)	284/702 (40)
At 5 min	60/715 (8)	64/703 (9)

P not significant for all between-group comparisons. Plus-minus values are means ± SD.
* Defined as birth weight <10th percentile for gestational age.[27]

TABLE 2. Randomization and Intake of Study PN

	Glutamine Group (n = 721)	Control Group (n = 712)	P Value
Hours from birth to randomization	38.1 ± 19.7	38.5 ± 18.8	.56
Days from birth to study PN	2.98 ± 1.09	3.00 ± 0.96	.61
Average amino acid intake in first 14 d of study PN, g/kg per day	2.23 ± 0.53	2.24 ± 0.57	.87
Day of life received 3 g/kg per day amino acids	9.9 ± 7.8	9.9 ± 8.4	.77

Plus-minus values are means ± SD.

TABLE 3. Primary Outcome of Death or Late-Onset Sepsis

Outcome	Glutamine (n = 721)	Control (n = 712)	RR (95% CI)	P Value
Death or late-onset sepsis, n (%)				
All infants	370 (51)	343 (48)	1.07 (0.97, 1.17)	.18
Birth weight, 401–750 g	206/325 (63)	197/322 (61)		
Birth weight, 751–1000 g	164/395 (42)	146/390 (37)		
Death, n (%)	124 (17)	127 (18)	0.97 (0.78, 1.21)	.75
Late-onset sepsis, n (%)	301 (42)	273 (38)	1.10 (0.98, 1.24)	.13
No. of episodes				.08
1	198 (27)	188 (26)		
2	62 (9)	51 (7)		
3	25 (3)	15 (2)		
≥ 4	10 (1)	5 (1)		

TABLE 4. Secondary Outcomes

Outcome	Glutamine (n = 721)	Control (n = 712)	RR (95% CI)	P Value
Proven necrotizing enterocolitis, n (%)				
All infants	69 (10)	68 (10)	0.99 (0.71, 1.40)	.99
Birth weight, 401–750 g	37/325 (11)	27/322 (8)		.20
Birth weight, 751–1000 g	32/396 (8)	41/390 (11)		.24
Surgical necrotizing enterocolitis, n/total n (%)	39/69 (57)	33/68 (49)	1.14 (0.90, 1.44)	.19
Days on ventilator	26.4 ± 26.4	26.0 ± 26.6		.84
Length of hospitalization, median days (5th, 95th percentile)				
Infants who survived	89 (49, 184)	90 (54, 159)		.49
Infants who died	18 (2, 145)	15 (2, 160)		.70

Plus-minus values are means ± SD.

tractive potential therapy for extremely premature infants who undergo extreme increases in metabolic demand and are at high risk for infection and feeding complications in the neonatal period. Clinical use of parenteral glutamine has been limited to date because of problems with solubility. In this trial, we overcame problems associated with glutamine instability in PN and increased plasma glutamine concentrations in extremely preterm infants without apparent biochemical risk, but we were unable to demonstrate a reduction in the risk of death or late-onset sepsis. Thus, routine use of parenteral glutamine as administered in this study in ELBW infants cannot be recommended.

Glutamine has several unique properties that suggest an important role in immunity, metabolism, and intestinal function. It is the most abundant amino acid in human plasma and milk,[1] and, in utero, is taken up by the developing mammalian fetus in greater quantity than any other amino acid.[11] Although glutamine is not an essential amino acid, there is growing evidence that the capacity to adequately increase de novo glutamine synthesis may be challenged during stress and critical illness.[12] In addition, glutamine is consumed as a primary substrate in large quantity by replicating cells including lymphocytes, fibroblasts, enterocytes, and tumor cells.[13–15] These properties provide strong rationale for the studies of glutamine supplementation in critically ill adults and animal models, many of which have demonstrated improved survival and decreased infection.[2,3,16,17] Furthermore, in both human and animal investigations, glutamine has been found to enhance gut integrity, improve gut immune function, and decrease bacterial translocation.

Placental supply of glutamine is terminated abruptly by preterm birth, and glutamine is not present in currently available amino acid solutions. One previous study in premature infants, although limited by a small sample size, suggested shorter time to reach full enteral feedings, fewer days on PN, and a tendency toward shorter length of hospital stay in a <800-g birth weight cohort of infants who received parenteral glutamine supplementation.[18] In addition, a small trial of enteral glutamine supplementation in premature infants demonstrated a decreased incidence of sepsis and improved tolerance of enteral feedings.[19]

We designed a trial of early parenteral glutamine rather than a trial of enteral glutamine for several

TABLE 5. Nutritional Outcomes

Outcome	Glutamine	Control	*P* Value
Days to first enteral feed			
All infants	7.5 ± 6.3	7.7 ± 6.7	.55
Birth weight, 401–750 g	9.7 ± 8.2	9.5 ± 7.8	.52
Birth weight, 751–1000 g	5.9 ± 3.6	6.4 ± 5.4	.75
Days to full enteral feeds			
All infants	34.8 ± 20.4	35.1 ± 21.2	.74
Birth weight, 401–750 g	42.1 ± 22.0	42.0 ± 24.1	.50
Birth weight, 751–1000 g	29.8 ± 17.5	30.2 ± 17.4	.68
Days of PN			
All infants	32.1 ± 23.5	29.8 ± 20.5	.05*
Birth weight, 401–750 g	37.9 ± 24.5	33.3 ± 21.8	.02*
Birth weight, 751–1000 g	27.5 ± 21.5	27.0 ± 18.8	.65
Feeding intolerance, *n*/total *n* (%)			
All infants	224/719 (31)	216/710 (30)	.74
Birth weight, 401–750 g	107/324 (33)	102/322 (32)	.71
Birth weight, 751–1000 g	117/395 (30)	114/388 (29)	.94
No. episodes (%)			.76
1	148 (66)	140 (65)	
2	39 (17)	52 (24)	
≥3	37 (17)	24 (11)	
Days to reach 1500 g			
Birth weight, 401–750 g	70.2 ± 16.4	68.6 ± 14.4	.28
Birth weight, 751–1000 g	49.3 ± 12.1	48.9 ± 11.7	.47
Weight at 36 weeks' postmenstrual age			
Birth weight, 401–750 g	1599 ± 358	1660 ± 345	.06
Birth weight, 751–1000 g	1833 ± 366	1872 ± 359	.17

Plus-minus values are means ± SD.

TABLE 6. Safety

Outcome	Glutamine	Control	*P* Value
Maximum serum urea nitrogen, mg/dL	31 ± 18	28 ± 16	.0008
Infants with serum urea nitrogen > 40 mg/dL	147/675 (22)	115/651 (18)	.06
Glutamine	*n* = 72	*n* = 69	
Baseline, μmol/L	291 (201–380)	316 (249–430)	
Study PN, μmol/L	381 (290–537)*	316 (230–383)	.0003†
Glutamate			
Baseline, μmol/L	30 (20–51)	37 (25–87)	
Study PN, μmol/L	53 (37–76)*	56 (41–92)*	.13†
Ammonia			
Baseline, μmol/L	66 ± 31	68 ± 25	
Study PN, μmol/L	77 ± 44	64 ± 41*	.023†

Plus-minus values are means ± SD; amino acid data are presented as median (interquartile range).
* $P < .05$ for within treatment group change between baseline and study PN sample.
† Test of treatment effect from a general linear model including terms for center and birth weight stratum, as applied to pre-post differences of the log of the relative changes.

reasons. Our previous research indicated that extremely preterm infants are at the highest risk for death and late-onset sepsis in the first month of life.[8,20] A parenteral route ensured early and constant provision of glutamine to our extremely premature patients, who depended on the parenteral route of nutrition for an average of 30 days after birth. Parenteral glutamine also allowed us to avoid the confounding that would have resulted from practice variability associated with enteral feedings and the high concentration of glutamine in human milk.

Given the overwhelming evidence that early provision of intravenous amino acids can limit catabolism in extremely premature infants,[21,22] our goal was early, aggressive delivery of intravenous amino acids. Although this trial resulted in earlier amino acid delivery at most of the participating centers, infants in both groups, on average, did not receive 3 g/kg per day of amino acids until 10 days of age. By this point in time, most also were receiving small volumes of enteral feeds; therefore, it is possible that we did not consistently deliver a sufficient dose of glutamine to demonstrate an effect in this high-risk group. Conversely, plasma glutamine concentrations increased significantly in infants in the glutamine group and were comparable to healthy, breastfed, term infants[23] and to the level achieved in a previous clinical trial of glutamine supplementation in premature infants.[18] Because PN was continued for the first month of life in the vast majority of infants, it is unlikely that the duration of supplementation is responsible for the negative results.

Given the near-linear relationship between nitrogen intake and nitrogen retention, the study amino acid solution was designed to be isonitrogenous with TrophAmine. Consequently, the substitution of 20% of the standard amino acids with glutamine may have unmasked other limitations in the currently

available solutions. Although there was no difference in the plasma concentration of total essential amino acids between the groups, infants in the glutamine group had a significantly greater decrease in plasma tyrosine (widely considered to be conditionally essential in premature infants) in response to study PN than did the control group.[7] However, there was no change in whole-body protein synthesis or turnover in a subset of infants,[24] and there was no difference in weight at 36 weeks' postmenstrual age between the groups, suggesting that overall amino acid supply was not limited by the substitution with 20% glutamine in the study amino acid solution.

Although we hypothesized that the infants who received parenteral glutamine would require fewer days on PN because of enhanced gut integrity and decreased bacterial translocation through the gut, the trend in the current study was that the infants who received glutamine actually required more days of PN support. In contrast to adults, it is possible that an enteral intervention is necessary to enhance gut integrity in premature infants. This concept is supported by the protective effect of breast milk against necrotizing enterocolitis.[25] However, Vaughn et al[26] recently completed a randomized trial of enteral glutamine supplementation in 649 infants with birth weights between 500 and 1250 g and found no reduction in nosocomial sepsis in the infants who received glutamine.

The obvious question is: Why are our findings in contrast to previous studies, particularly the large, randomized, clinical trials in bone marrow transplant recipients and critically ill adults? We chose to enroll extremely premature infants, because this population is at significant risk of mortality and morbidity from late-onset sepsis.[8] However, the organisms responsible for sepsis in neonates are different from those in adults. It is possible also that deficiencies in the immune system predisposing premature neonates to sepsis may not be amenable to a nutritional intervention such as glutamine supplementation.

Developmental differences between adults and immature neonates also may have contributed to the different outcome in our population. The pathophysiology of illness and the ability to compensate for glutamine deficiency may be different in these groups. The amino acid solutions used in the current study supplied glutamate (as did the clinical trials in adults). To the extent that glutamate is converted to glutamine, these patients may not have been truly glutamine deficient, particularly because PN was initiated so early. This would be in contrast to the studies in adults, in which the subjects were nutritionally depleted and catabolic. In addition, our study design was a preventative measure, whereas the majority of the adult trials enrolled critically ill subjects.

Although parenteral glutamine supplementation seems to be well tolerated in extremely premature neonates, we cannot advocate its routine use currently, given the lack of clinical efficacy in this randomized, clinical trial. Future studies are needed to determine whether glutamine supplementation may be of benefit to other subsets of critically ill neonates.

ACKNOWLEDGMENTS

This work was supported by cooperative agreements with the National Institute of Child Health and Human Development (U10 HD27856 [Dr Lemons], U10 HD27871 [Dr Ehrenkranz], U10 HD27851 [Dr Stoll], U10 HD36790 [Dr Poole], U10 HD27904 [Dr Oh], U10 HD21397 [Dr Bauer], U10 HD27881 [Dr Papile], U10 HD21373 [Dr Tyson], U10 HD34216 [Dr Carlo], U10 HD40689 [Dr Laptook], U10 HD27853 [Dr Donovan], U10 HD27880 [Dr Stevenson], U10 HD21364 [Dr Fanaroff], U10 HD21415 [Dr Korones], U10 HD21385 [Dr Shankaran], and U10 HD40461 [Dr Finer]) and General Clinical Research Centers grants M01 RR00750 (Indiana University), M01 RR 06022 (Yale University), M01 RR 00997 (University of New Mexico), M01 RR08084 (University of Cincinnati), and M01 RR00070 (Stanford University).

We are indebted to Drs Gordon Avery, Mary D'Alton, John Fletcher, Christine Gleason, Maureen Maguire, Carol Redmond, Charlotte Catz, and William Heird for their contribution as members of the data and safety monitoring committee; to Lisa Wrage for assistance with the statistical analyses; and to our medical and nursing colleagues and the infants and their parents, who participated in the study.

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APPENDIX 1. Members of the National Institute of Child Health and Human Development Neonatal Research Network (and National Institute of Child Health and Human Development Cooperative Agreements Numbers)

Alan Jobe, MD, PhD, Steering Committee Chairperson
University of Cincinnati

Waldemar A. Carlo, MD*
Namasivayam Ambalavanan, MD
Monica V. Collins, RN
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University of California at San Diego (U10 HD40461)

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Michele Walsh, MD
Nancy Newman, RN
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Vivek Narendran MD, MRCP
Marcia Mersmann, RN
University of Cincinnati (U10 HD27853 and M01 RR 08084)

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Lu-Ann Papile, MD*
Conra Backstrom, RN
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Betty Hastings
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Sheldon B. Korones, MD*
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Abbot R. Laptook, MD*
Susie Madison, RN
University of Texas Southwestern Medical Center (U10 HD40689)

Seetha Shankaran, MD*
Ganesh Konduri, MD
Geraldine Muran, RN
Wayne State University (U10 HD21385)

William Oh, MD*
Barbara Stonestreet, MD
Angelita Hensman, RN
Women and Infants Hospital (U10 HD27904)

Richard A. Ehrenkranz, MD*
Patricia Gettner, RN
Yale University (U10 HD27871 and M01 RR 06022)

* Principal Investigator.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Gordon, Valery (NIH/OD) [E]
Subject: RE: About SUPPORT
Date: Tuesday, April 23, 2013 4:49:00 PM
Attachments: Van Meurs, Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure, NEJM, 07-2005.pdf

Here is the nitric oxide in preemies paper – we did not do a press release that I can find for this one.

Rose

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From: Gordon, Valery (NIH/OD) [E]
Sent: Tuesday, April 23, 2013 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: About SUPPORT

Thank you very much.

1. We want to write a paragraph that starts with: (b)(5)

   (b)(5)

   We asked for a couple of examples, but I think that the request was insufficiently clear. We need a couple (or 3) examples of (b)(5)

   (b)(5)

2. The next paragraph currently contains the following information: (b)(5)

   (b)(5)

   I obtained this information from protocols, publications, editorials, and letters. But was there

something significant about the 1950's? And what was meant by (b)(5)? Does it mean (b)(5) Is there more (b)(5) And what happened after the 1950's? I found meta-analyses conducted between 2000 and 2009 (Cochrane Database Syst. Rev.). But surely something was done between 1950 and 2000?

These are the issues for which we need information at the moment.
If it is easier to talk with me on the phone, I provide my direct number below.

I appreciate your assistance with this project and your willingness to share your expertise.
Valery

Valery Gordon Ph.D., M.P.H.

Acting Director, Clinical Research Policy,

Office of Science Policy, OD

NIH

(301) 402-7667 (direct phone)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, April 23, 2013 2:16 PM
To: Gordon, Valery (NIH/OD) [E]
Subject: RE: About SUPPORT

That is fine.
Happy to try to answer any questions

Best regards
Rose

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From: Gordon, Valery (NIH/OD) [E]
Sent: Tuesday, April 23, 2013 2:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: About SUPPORT

Hello Rosemary,
I don't think we've met, but I am part of the OSP team that is drafting an editorial for the NIH Director. The editorial is about research with pre-term infants and uses the SUPPORT study as an example of valuable research that has informed the care of these infants.
We have been working through Mona Rowe, who has obtained information from you and then passed it back to us. I can continue to use this pathway if this is best, or if it would be OK, I wonder if I can ask you a few questions that will help us to complete a draft of this document.
Would you please let me know?
Thank you,
Valery

Valery Gordon Ph.D., M.P.H.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2005 VOL. 353 NO. 1

Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure

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ABSTRACT

BACKGROUND

Inhaled nitric oxide is a controversial treatment for premature infants with severe respiratory failure. We conducted a multicenter, randomized, blinded, controlled trial to determine whether inhaled nitric oxide reduced the rate of death or bronchopulmonary dysplasia in such infants.

METHODS

We randomly assigned 420 neonates, born at less than 34 weeks of gestation, with a birth weight of 401 to 1500 g, and with respiratory failure more than four hours after treatment with surfactant to receive placebo (simulated flow) or inhaled nitric oxide (5 to 10 ppm). Infants with a response (an increase in the partial pressure of arterial oxygen of more than 10 mm Hg) were weaned according to protocol. Treatment with study gas was discontinued in infants who did not have a response.

RESULTS

The rate of death or bronchopulmonary dysplasia was 80 percent in the nitric oxide group, as compared with 82 percent in the placebo group (relative risk, 0.97; 95 percent confidence interval, 0.86 to 1.06; P=0.52), and the rate of bronchopulmonary dysplasia was 60 percent versus 68 percent (relative risk, 0.90; 95 percent confidence interval, 0.75 to 1.08; P=0.26). There were no significant differences in the rates of severe intracranial hemorrhage or periventricular leukomalacia. Post hoc analyses suggest that rates of death and bronchopulmonary dysplasia are reduced for infants with a birth weight greater than 1000 g, whereas infants weighing 1000 g or less who are treated with inhaled nitric oxide have higher mortality and increased rates of severe intracranial hemorrhage.

CONCLUSIONS

The use of inhaled nitric oxide in critically ill premature infants weighing less than 1500 g does not decrease the rates of death or bronchopulmonary dysplasia. Further trials are required to determine whether inhaled nitric oxide benefits infants with a birth weight of 1000 g or more.

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*Members of the Preemie Inhaled Nitric Oxide Study, which is part of the NICHD Neonatal Research Network, are listed in the Appendix.

N Engl J Med 2005;353:13-22.

PREMATURE INFANTS IN RESPIRATORY failure can have dramatic improvements after treatment with exogenous surfactant. However, a subset of premature infants have suboptimal responses to surfactant[1] and may have pulmonary hypertension in association with severe respiratory failure.[2-6] Inhaled nitric oxide may benefit such infants by selectively dilating pulmonary vasculature, improving ventilation–perfusion matching, and decreasing the pulmonary inflammatory response.[7-9]

Inhaled nitric oxide had been shown to provide only short-term improvement in oxygenation in premature infants[10-14] until a recent single-center study reported an association between the administration of inhaled nitric oxide and a decrease in the incidence of bronchopulmonary dysplasia or death in a cohort of moderately ill infants.[15] We hypothesized that inhaled nitric oxide administered to premature infants with severe respiratory failure would reduce the incidence of death or bronchopulmonary dysplasia.

METHODS

HYPOTHESES AND OUTCOMES

The primary hypothesis was that administration of inhaled nitric oxide to neonates at less than 34 weeks of gestation, with a birth weight of 401 to 1500 g, and with severe respiratory failure would reduce the incidence of bronchopulmonary dysplasia or death (defined as death before discharge to home or within 365 days among hospitalized infants). Severe respiratory failure was defined as an oxygenation index of 10 or more on two consecutive measurements of arterial blood gases between 30 minutes and 12 hours apart. We used the conventional definition of bronchopulmonary dysplasia — treatment with oxygen at 36 weeks of gestation.[16] The oxygenation index was calculated as 100 × the fraction of inspired oxygen × the mean airway pressure (in centimeters of water) ÷ the partial pressure of arterial oxygen (PaO_2) (in millimeters of mercury).

The secondary hypotheses were that inhaled nitric oxide would not increase the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, and that it would decrease the number of days of assisted ventilation and oxygen use, the length of hospitalization, and the incidence of threshold retinopathy of prematurity.[17] In addition to the conventional definition of bronchopulmonary dysplasia, we assessed the "physiological requirement" for oxygen at 36 weeks of gestation in infants not on mechanical ventilation and receiving less than 30 percent oxygen by performing a stepwise reduction in oxygen delivery to the lowest oxygen concentration at which the oxygen saturation measured by pulse oximetry remained at least 90 percent.[18] Infants who were unable to maintain a saturation of 90 percent or more while breathing room air were classified as requiring supplemental oxygen and therefore having "physiological bronchopulmonary dysplasia."

CRITERIA FOR ELIGIBILITY

Neonates who had been born at less than 34 weeks of gestation, according to the best obstetric estimate, had a birth weight of 401 to 1500 g, required assisted ventilation, and had a diagnosis of respiratory distress syndrome, sepsis or pneumonia, aspiration syndrome, idiopathic persistent pulmonary hypertension, or suspected pulmonary hypoplasia were eligible. Eligible infants had received one dose of surfactant at least 4 hours before meeting the respiratory criteria for entry and had an oxygenation index of at least 10 on two consecutive measurements of arterial blood gas between 30 minutes and 12 hours apart.

On the basis of pilot data collected in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers, we estimated that the rate of mortality or bronchopulmonary dysplasia in infants identified by the oxygenation-index criterion would be 75 percent. At the first interim analysis of the data safety and monitoring committee, the mortality rate was significantly higher than expected in both treatment groups. The committee requested that the entry criteria be modified to select a cohort whose severity of illness as measured by the oxygenation index was more similar to that of the targeted cohort. Data from the NICHD Neonatal Research Network were analyzed and used to revise the respiratory criteria for entry to an oxygenation index of at least 5 followed by an oxygenation index of at least 7.5, with the second determination made 30 minutes to 24 hours after the first. Hence, for purposes of analysis, the design was considered to have two strata based on the oxygenation-index entry criterion. Infants who required an indwelling arterial line were eligible from 4 to 120 hours after birth.

Infants were ineligible if they had congenital heart disease other than ventricular septal defect,

atrial-level shunt, or patent ductus arteriosus; any major congenital abnormality involving the respiratory system; thrombocytopenia (a platelet count ≤50,000 per cubic millimeter); or bleeding diathesis or if a decision had been made not to provide full treatment. The study was approved by the institutional review board of each study center, and written informed consent was obtained from the parents or guardians of all infants.

Clinical care was not mandated by the protocol, but each center agreed to its own management guidelines to define its approach to mean arterial pressure, partial pressure of carbon dioxide, pH, surfactant replacement therapy, high-frequency ventilation, targets for lung inflation, paralysis, and the use of indomethacin, corticosteroids, bronchodilators, sedation, anesthesia, and analgesia for the duration of the trial.

STUDY DESIGN AND RANDOMIZATION

A dedicated telephone system developed by the data center stratified infants according to center and birth weight (401 to 750 g, 751 to 1000 g, and 1001 to 1500 g). Infants were randomly assigned within each stratum, according to a permuted-block design, to receive inhaled nitric oxide or placebo. Randomization, administration of the study gas, and safety monitoring were performed by designated, nonblinded persons not involved in clinical care. To maintain blinding, they made mock adjustments in the control infants, used a proprietary delivery and monitoring unit (INOvent, Datex-Ohmeda) with a specially designed gauge cover secured with a numbered tether (to keep track of when and by whom the unit had been opened), used an oxygen analyzer upstream of the site of administration of the study gas, and covered the downstream oxygen analyzer. A shroud secured with tamper-resistant tape was used to cover the tank label, and a screen was used to ensure blinding when the gauge cover was opened. All other research and clinical personnel were blinded to the treatment assignment.

ADMINISTRATION OF STUDY GAS

The study protocol was based on previous trials of inhaled nitric oxide performed by the Neonatal Research Network.[19,20] When a study candidate had an initial measurement of arterial blood gas with a qualifying oxygenation index, parental consent was obtained, and an unblinded respiratory therapist set up the delivery system and analyzer (INOvent, Datex-Ohmeda) according to the manufacturer's guidelines. When a second qualifying measurement of arterial blood gas was obtained, infants were randomly assigned to either 5 ppm inhaled nitric oxide (INOmax, INO Therapeutics) or simulated flow. Primary-grade nitric oxide was supplied in a concentration of 800 ppm in nitrogen certified to be within ±1 percent of the stated nitric oxide content and to contain less than 5 ppm of nitrogen dioxide. If the study gas could not be initiated within 15 minutes, an additional sample of arterial blood gas was drawn as a baseline measurement and used to calculate the response to the study gas.

Response to the study gas was defined by the change in the PaO_2 between the baseline measurement and the measurement at 30 minutes without any alterations in ventilator or oxygen settings. A complete response was an increase of more than 20 mm Hg, a partial response an increase of 10 to 20 mm Hg, and no response an increase of less than 10 mm Hg. When a complete response occurred, administration of the same concentration of study gas was continued. For infants with less than a complete response, the study gas was increased to 10 ppm of inhaled nitric oxide or simulated flow, and arterial blood gas was measured again 30 minutes later. Infants who had a complete or partial response to 10 ppm of inhaled nitric oxide continued to be given that concentration; the study gas was discontinued in infants with no response at this flow level. If the condition of the infant deteriorated during administration of the initiation dose of the study gas, administration was discontinued and stabilization of the patient was attempted by such means as adjustment of the ventilator settings or inotropic infusions. If the patient was successfully stabilized, initiation of the study gas was tried again. If treatment with the study gas at the initiation dose was again accompanied by complications, the patient was classified as not having a response, and the study gas was withdrawn.

Weaning of the infants from the study gas followed a defined protocol and occurred 10 to 14 hours after the treatment had been initiated. Weaning was attempted only when the PaO_2 was more than 50 mm Hg and the oxygen saturation measured by pulse oximetry was greater than 90 percent. For weaning, the concentration of nitric oxide in the inhaled gas (or the simulated flow) was reduced as follows: 10.0, 5.0, 4.0, 3.0, 2.0, 1.0, 0.5, 0.0 ppm. If the oxygenation index was 5 or less, weaning was attempted every four to eight hours. Successful weaning was defined as a decrease in

the PaO_2 of less than 20 mm Hg and to a value no lower than 50 mm Hg and oxygen saturation greater than 90 percent in the 30 minutes after the weaning attempt.

The dose of the study gas could be increased if two consecutive oxygenation indexes measured 30 minutes apart were at least 7.5. The study gas could be reinitiated if the original entry criteria were met and if no more than 72 hours had passed since the study gas was discontinued. The maximal duration of the administration of the study gas was 336 hours, and the dose could not exceed 1 ppm after 240 hours.

SAFETY MONITORING

Blood methemoglobin concentrations were measured within the first 3 hours after administration of the study gas, and then after 12 and 24 hours. While the infants were receiving nitric oxide at a concentration of more than 5 ppm, the sampling interval was every 24 hours, and while they were receiving a concentration of less than 5 ppm, the interval was every 48 hours. Methemoglobin levels of 4 percent or more were managed by reducing the concentration of study gas by half until the level fell below 4 percent. The study gas was discontinued if the methemoglobin concentration exceeded 10 percent.

Continuous inhaled nitrogen dioxide concentrations were monitored, and if they exceeded 3 ppm, the delivery system was immediately checked and infants were weaned from the study gas in 50 percent increments until the concentration was below 3 ppm. If the concentration exceeded 5 ppm, the nitric oxide cylinder was changed; the study gas was discontinued if nitrogen dioxide concentrations remained greater than 5 ppm. Cranial ultrasound scans were performed on all infants at 28±3 days.

STATISTICAL ANALYSIS

Assuming an incidence of death or bronchopulmonary dysplasia of 75 percent, we determined that 220 infants would be required in each group to provide the study with 90 percent power to detect a reduction in death or bronchopulmonary dysplasia of 20 percent in the group given inhaled nitric oxide. All tests were two-tailed, with an alpha level of 0.05. We conducted the primary analysis according to the intention-to-treat principle.

Differences between the treatment groups in baseline characteristics, status at randomization, and response to study gas were tested with the use of t-tests for continuous variables and chi-square tests for categorical variables. Differences in the primary and secondary outcomes were tested with the use of Poisson regression models for categorical variables and linear regression models for continuous variables. The models included birth-weight category, oxygenation-index stratum, center, and treatment group and were used to calculate the adjusted relative risks and 95 percent confidence intervals.[21] The post hoc analysis used the same model (when appropriate) as the primary analysis, and the interactions were tested by adding the relevant variables to the model.

The interim analyses of the data safety and monitoring committee were performed after one third and two thirds of the study patients had reached an end point of the study. The efficacy stopping rule for the study was based on the O'Brien–Fleming boundary, with three analyses of the data for the primary outcome one third of the way through the study, two thirds of the way through, and at the conclusion of the trial. The nominal significance level was 0.05, and corresponding P values for the looks were 0.005, 0.01, and 0.04, respectively.[22]

INO Therapeutics provided the study gas, gas delivery systems, and site monitoring for all hospitals and capitation funding for the hospitals outside the NICHD Neonatal Research Network. The company was otherwise not involved in the study design, data analysis and interpretation, or preparation of the manuscript.

RESULTS

RECRUITMENT

At the recommendation of the data safety and monitoring committee, the trial was terminated after the second planned interim analysis, with 294 (67 percent) of the enrolled infants having reached a study end point (death, discharge to home, or 365 days of age). At that time, the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia was significantly higher in the group being given inhaled nitric oxide than in the control group, and there was no apparent beneficial effect of treatment on the primary outcome. Recruitment ceased with enrollment of 420 patients instead of the planned enrollment of 440.

BASELINE CHARACTERISTICS AND STATUS AT RANDOMIZATION

From January 4, 2001, to September 26, 2003, 420 infants were enrolled in the trial. There were no sig-

nificant differences between treatment groups in the baseline characteristics (Table 1) or status at the time of randomization (Table 2). The distribution by birth weight did not differ significantly between the two treatment groups, with an overall distribution of 47 percent in the infants who weighed 401 to 750 g, 28 percent in those who weighed 751 to 1000 g, and 25 percent in those who weighed 1001 to 1500 g. The mean (±SD) oxygenation index at randomization was 24.6±16.3 for the first oxygenation-index stratum, and 20.4±17.4 for the second stratum.

The baseline characteristics for eligible infants who did not undergo randomization were similar to those for enrolled infants. The reasons for not enrolling were refusal of the parent (31 percent); unavailability of the parent (5 percent); or consent not being sought because of the recommendation of the attending physician (17 percent), unavailability of equipment (9 percent), use of high-frequency jet ventilation (8 percent), or other reasons (30 percent).

Table 1. Baseline Characteristics of the Infants.*

Characteristic	Inhaled Nitric Oxide (N=210)	Placebo (N=210)
Birth weight — g	840±264	837±260
Gestational age — wk	26±2	26±2
Male sex — no. (%)	133 (63)	127 (60)
Mother's race or ethnic group — no. (%)†		
White	95 (45)	96 (46)
Black	69 (33)	78 (37)
Hispanic	36 (17)	32 (15)
Other	10 (5)	4 (2)
Born at study hospital — no. (%)	165 (79)	159 (76)
Prenatal corticosteroids — no. (%)‡	119 (70)	114 (67)
Delivery by cesarean section — no. (%)	144 (69)	139 (66)
Apgar scores <4 at 1 min — no. (%)‡	92 (55)	87 (52)
Apgar scores <4 at 5 min — no. (%)‡	27 (16)	22 (13)
Cause of respiratory failure — no. (%)		
Respiratory distress syndrome	192 (91)	190 (90)
Sepsis or pneumonia	6 (3)	10 (5)
Aspiration syndromes	1 (<1)	0
Idiopathic persistent pulmonary hypertension of the newborn	6 (3)	5 (2)
Suspected pulmonary hypoplasia	5 (2)	5 (2)

* Plus–minus values are means ±SD.
† Race or ethnic group was self-reported.
‡ Data were not available for all infants.

Table 2. Status of Infants at Randomization.*

Status	Inhaled Nitric Oxide (N=210)	Placebo (N=210)
Age — hr	26±23	28±22
Oxygenation index†	23±17	22±17
Surfactant — no. of doses given	2±1	2±1
Type of ventilation — no. (%)		
High-frequency oscillatory ventilation	116 (55)	116 (55)
High-frequency flow interruption	9 (4)	8 (4)
Conventional mechanical ventilation	85 (40)	86 (41)
Inotropic support — no. (%)	127 (60)	126 (60)
Sedation or analgesia — no. (%)	155 (74)	150 (71)
Paralytic agents — no. (%)	31 (15)	25 (12)
Postnatal corticosteroids — no. (%)	20 (10)	22 (10)
Pulmonary air leaks — no. (%)	26 (12)	31 (15)
Pulmonary hemorrhage — no. (%)	22 (10)	15 (7)
Seizures — no. (%)	8 (4)	6 (3)

* Plus–minus values are means ±SD.
† The oxygenation index was calculated as 100 × the fraction of inspired oxygen × mean airway pressure (in centimeters of water) ÷ the partial pressure of arterial oxygen (in millimeters of mercury).

PRIMARY OUTCOME

There was no difference between the incidence of the primary outcome (bronchopulmonary dysplasia or death) between the group given inhaled nitric oxide and the placebo group (80 percent vs. 82 percent; relative risk, 0.97; 95 percent confidence interval, 0.86 to 1.06; P=0.52) (Table 3). The rate of bronchopulmonary dysplasia was 60 percent in the group given inhaled nitric oxide and 68 percent in the placebo group (relative risk, 0.90; 95 percent confidence interval, 0.75 to 1.08; P=0.26), and the rate of death was 52 percent in the group given inhaled nitric oxide and 44 percent in the placebo group (relative risk, 1.16; 95 percent confidence interval, 0.96 to 1.39; P=0.11). There were no discernible differences between the group given inhaled nitric oxide and the placebo group for the following variables: age at death (20 vs. 24 days, P=0.54) or cause of death (respiratory failure, 49 percent vs. 42 percent; neurologic insult, 4 percent vs. 1 percent; infection, 5 percent vs. 10 percent; necrotizing enterocolitis, 8 percent vs. 2 percent; support withdrawn, 19 percent vs. 26 percent; or other, 16 percent vs. 19 percent; P=0.13 for the equality of the distribution between the two treatment groups).

SECONDARY OUTCOMES

The frequency of severe intraventricular hemorrhage or periventricular leukomalacia was not sig-

Table 3. Primary and Secondary Outcomes.*

Outcome	Inhaled Nitric Oxide (N=210)	Placebo (N=210)	Relative Risk (95% CI)†	P Value
Primary — no. (%)				
Death or bronchopulmonary dysplasia‡	167 (80)	170 (82)	0.97 (0.86–1.06)	0.52
Death	109 (52)	93 (44)	1.16 (0.96–1.39)	0.11
Bronchopulmonary dysplasia§	65 (60)	86 (68)	0.90 (0.75–1.08)	0.26
Secondary				
Grade 3 or 4 IVH or PVL — no. (%)¶	69 (39)	50 (32)	1.25 (0.95–1.66)	0.11
Oxygen use — days‖	84±63	91±61		0.91
Physiological bronchopulmonary dysplasia — no. (%)**	50 (50)	69 (60)	0.87 (0.68–1.10)	0.17
Length of hospitalization — days‖	101±47	111±48		0.65
Duration of ventilation — days‖	39±45	47±53		0.56
Incidence of air leak — no. (%)‖	35 (35)	37 (32)	1.12 (0.78–1.61)	0.55
Threshold retinopathy of prematurity — no. (%)††	29 (30)	36 (32)	1.16 (0.81–1.64)	0.42

* Plus–minus values are means ±SD. CI denotes confidence interval, IVH intraventricular hemorrhage, and PVL periventricular leukomalacia.
† Values were adjusted for center, birth-weight group, and oxygenation-index entry stratum.
‡ The outcome of death or bronchopulmonary dysplasia is for 208 infants in the placebo group.
§ This outcome is for infants who were alive at 36 weeks (109 in the group receiving inhaled nitric oxide and 127 in the placebo group).
¶ Results of ultrasound examinations of the head were available for 179 infants in the group receiving inhaled nitric oxide and for 155 in the placebo group.
‖ This outcome is for infants who survived (101 in the group receiving inhaled nitric oxide and 117 in the placebo group).
** This outcome was defined according to the protocol of Walsh et al.,[18] for 100 infants in the group receiving inhaled nitric oxide and for 115 infants in the placebo group.
†† Examination for retinopathy of prematurity was performed in 98 infants in the group receiving inhaled nitric oxide and 112 infants in the placebo group.

nificantly different between the group given inhaled nitric oxide and the placebo group according to concurrent local radiology readings (39 percent vs. 32 percent, respectively; relative risk, 1.25; 95 percent confidence interval, 0.95 to 1.66; P=0.11) (Table 3) or by central reading performed after the trial was terminated (37 percent vs. 38 percent; relative risk, 0.97; 95 percent confidence interval, 0.74 to 1.27; P=0.81). The local reading was based on the worst results of evaluation among ultrasound examinations of the head performed during the administration of the study gas, at 28±3 days, and after 28 days of age. Ultrasound examinations of the head were not available for 86 infants, 93 percent of whom had died. Death occurred by 14 days in 91 percent and before 28 days in 98 percent. The central reading was based on the worst results of evaluation among all ultrasound examinations of the head performed during hospitalization. There were no significant differences in the two treatment groups with respect to the days on oxygen, the length of assisted ventilation, the length of hospitalization, the incidence of air leak, threshold retinopathy of prematurity, or "physiological bronchopulmonary dysplasia" for survivors (Table 3).

Thirty minutes after administration of the study gas, at a concentration of 5 ppm, the group given inhaled nitric oxide had a significant increase in the PaO_2 and a significant decrease in the oxygenation index as compared with the placebo group (Table 4). The PaO_2 and the oxygenation index showed no significant change in either group when the concentration of the study gas was increased to 10 ppm. More than 70 percent of the infants in the placebo group did not have a response to the study gas; these infants had a significantly shorter length of time on the study gas (39 vs. 76 hours).

There were 26 deviations from the protocol. Five ineligible infants were randomly assigned to a study group. One infant received the wrong study gas. Four incidents of unblinding occurred. Sixteen infants received open-label inhaled nitric oxide: sev-

en after undergoing randomization to inhaled nitric oxide and nine after undergoing randomization to placebo.

SAFETY AND TOXICITY

In the group given inhaled nitric oxide, two infants had a methemoglobin level of at least 4 percent, and one had a level of at least 8 percent. In the placebo group, two infants had a methemoglobin level of at least 4 percent; neither received open-label inhaled nitric oxide. In the group given inhaled nitric oxide, nitrogen dioxide concentrations were at least 3 ppm in four infants and at least 5 ppm in two infants. No infants in the placebo group had elevated nitrogen dioxide concentrations (Table 4).

POST HOC ANALYSES

Post hoc analyses evaluated the relationship among birth weight (≤1000 g or >1000 g), mode of ventilation (high-frequency ventilation or conventional mechanical ventilation), severity of illness (as measured by a median oxygenation index >17 vs. ≤17) in terms of the primary outcomes, and the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia (Table 5). The interaction between treatment assignment and birth weight had a significant effect on death (P=0.02) as well as on death or bronchopulmonary dysplasia (P=0.02).

Infants with a birth weight above 1000 g who were treated with inhaled nitric oxide had a significantly lower rate of death or bronchopulmonary dysplasia than infants in the placebo group (50 percent vs. 69 percent; relative risk, 0.72; 95 percent confidence interval, 0.54 to 0.96; P=0.03). Infants with a weight of 1000 g or less who were treated with inhaled nitric oxide, as compared with those in the placebo group, had higher mortality (62 percent vs. 48 percent; relative risk, 1.28; 95 percent confidence interval, 1.06 to 1.54; P=0.01) and a higher rate of severe intraventricular hemorrhage (43 percent vs. 33 percent; relative risk, 1.40; 95 percent confidence interval, 1.03 to 1.88; P=0.03).

The interaction between treatment group and type of ventilation had a significant effect on mortality (P=0.03). Infants receiving inhaled nitric oxide by means of conventional mechanical ventilation had a significantly increased rate of death as compared with infants receiving placebo by means of conventional mechanical ventilation (62 percent vs. 40 percent; relative risk, 1.46; 95 percent confidence interval, 1.10 to 1.92; P=0.01). Infants given inhaled nitric oxide as compared with those given placebo by means of conventional mechanical ventilation had similar oxygenation indexes at randomization (22.6±19.2 vs. 17.6±14.1, P=0.06) and similar birth weights (814±255 g vs. 853±267 g, P=0.33). The interaction between the treatment group and the oxygenation index was not significant.

Table 4. Response to Study Gas.*

Variable	Inhaled Nitric Oxide (N=210)	Placebo (N=210)	P Value
Response to concentrations of 5 ppm — no.	208	204	
Increase in PaO_2 — no. (%)			<0.001
<10 mm Hg	60 (29)	151 (74)	
10–20 mm Hg	30 (14)	18 (9)	
>20 mm Hg	118 (57)	35 (17)	
Change in PaO_2 — mm Hg	57±88	8±53	<0.001
Change in oxygenation index	−8±13	1±17	<0.001
Response to concentrations of 10 ppm — no.	86	152	
Increase in PaO_2 — no. (%)			0.24
<10 mm Hg	53 (62)	109 (72)	
10–20 mm Hg	18 (21)	26 (17)	
>20 mm Hg	15 (17)	17 (11)	
Change in PaO_2 — mm Hg	8±35	10±37	0.68
Change in oxygenation index	−3±15	−1±11	0.29
Duration of administration of study gas — hr†	76±73	39±65	<0.001
Methemoglobin level ≥4% — no. (%)	2 (1)	2 (1)	0.99
Methemoglobin level ≥8% — no. (%)	1 (<1)	0	0.99
Nitrogen dioxide concentration ≥3.0 ppm — no. (%)	4 (2)	0	0.13
Nitrogen dioxide concentration ≥5.0 ppm — no. (%)	2 (1)	0	0.50

* Plus–minus values are means ±SD. PaO_2 denotes the partial pressure of arterial oxygen.
† The duration was calculated only in infants with a response.

DISCUSSION

We found that the administration of inhaled nitric oxide as used in this trial for premature infants with severe respiratory failure did not reduce the combined incidence of death or bronchopulmonary dysplasia. There were no significant differences in the secondary outcomes.

Previous randomized trials of the use of inhaled

Table 5. Post Hoc Analysis According to Birth Weight, Type of Ventilation, and Oxygenation Index.*

Variable	Inhaled Nitric Oxide	Placebo	Relative Risk (95% CI)†	P Value
	no. (%)			
Birth weight				
≤1000 g	158	158		
Death or bronchopulmonary dysplasia	141 (89)	133 (85)	1.04 (0.96–1.13)	0.29
Death	98 (62)	76 (48)	1.28 (1.06–1.54)	0.01
Bronchopulmonary dysplasia	49 (73)	65 (73)	1.02 (0.85–1.23)	0.84
Grade 3 or 4 IVH or PVL	55 (43)	39 (33)	1.40 (1.03–1.88)	0.03
>1000 g	52	52		
Death or bronchopulmonary dysplasia	26 (50)	35 (69)	0.72 (0.54–0.96)	0.03
Death	11 (21)	17 (33)	0.65 (0.36–1.18)	0.16
Bronchopulmonary dysplasia	16 (38)	21 (57)	0.68 (0.45–1.05)	0.08
Grade 3 or 4 IVH or PVL	14 (27)	11 (30)	0.95 (0.53–1.69)	0.86
Type of ventilation				
Conventional mechanical ventilation	85	86		
Death or bronchopulmonary dysplasia	69 (81)	63 (74)	1.04 (0.91–1.19)	0.55
Death	53 (62)	34 (40)	1.46 (1.10–1.92)	0.01
Bronchopulmonary dysplasia	17 (52)	33 (60)	0.90 (0.65–1.24)	0.53
Grade 3 or 4 IVH or PVL	29 (43)	24 (36)	1.20 (0.80–1.78)	0.37
High-frequency ventilation	125	124		
Death or bronchopulmonary dysplasia	98 (78)	105 (85)	0.93 (0.84–1.04)	0.21
Death	56 (45)	59 (48)	0.96 (0.75–1.24)	0.75
Bronchopulmonary dysplasia	48 (63)	53 (75)	0.89 (0.72–1.10)	0.29
Grade 3 or 4 IVH or PVL	40 (36)	26 (30)	1.41 (0.96–2.08)	0.08
Oxygenation index				
≤17	100	110		
Death or bronchopulmonary dysplasia	71 (71)	83 (75)	0.93 (0.81–1.08)	0.37
Death	45 (45)	40 (36)	1.27 (0.96–1.68)	0.09
Bronchopulmonary dysplasia	30 (51)	50 (66)	0.80 (0.61–1.06)	0.12
Grade 3 or 4 IVH or PVL	30 (33)	27 (30)	1.18 (0.79–1.76)	0.42
>17	110	100		
Death or bronchopulmonary dysplasia	96 (87)	85 (86)	1.02 (0.92–1.12)	0.75
Death	64 (58)	53 (53)	1.11 (0.88–1.40)	0.39
Bronchopulmonary dysplasia	35 (70)	36 (72)	0.98 (0.77–1.24)	0.85
Grade 3 or 4 IVH or PVL	39 (45)	23 (35)	1.38 (0.97–1.96)	0.07

* Data were not available for all infants in the categories of bronchopulmonary dysplasia and grade 3 or 4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL). Some infants had bronchopulmonary dysplasia and died. CI denotes confidence interval.

† Values were adjusted for center, birth-weight group, and oxygenation-index stratum.

nitric oxide in premature infants have shown varied results. In a trial of 80 premature infants with severe hypoxemic respiratory failure, Kinsella et al. reported a decrease in the number of days on a ventilator and a trend toward a decreased incidence of bronchopulmonary dysplasia.[10] The Franco–Belgian randomized trial of inhaled nitric oxide showed no significant decrease in bronchopulmonary dysplasia or death in a cohort of premature infants with a median oxygenation index of approximately 20.[11,12] A recent trial by Schreiber et al. studied a less critically ill cohort with a median oxy-

genation index of 6.94 on mechanical ventilation after the use of surfactant.[15] A significant decrease in bronchopulmonary dysplasia or death and severe intracranial hemorrhage was reported, but the benefit was confined to the cohort with an oxygenation index below 6.94.

The results of our trial may seem to be inconsistent with those of the trial of Schreiber et al. However, the infants enrolled in our trial were smaller and sicker than those in the trial of Schreiber et al. Benefit in the Schreiber trial was limited to infants with an oxygenation index below 6.94, but only 17 infants in our trial had an oxygenation index in this range. Benefit (i.e., decreased bronchopulmonary dysplasia or death) in our trial was evident only in infants with a birth weight above 1000 g (Table 5), and the patients in the trial of Schreiber et al. had significantly higher birth weights than those in our trial. Their trial also had a larger proportion of black infants, but our analysis did not reveal a significant effect of race on responses to inhaled nitric oxide.

The rate of intraventricular hemorrhage has been a concern in trials of preterm infants given inhaled nitric oxide, because nitric oxide is known to inhibit platelet aggregation and increase bleeding time.[23-28] Two small pilot studies of the use of inhaled nitric oxide showed high rates of intraventricular hemorrhage,[29,30] but larger randomized controlled trials have not confirmed those findings.[10-15] Review of our data on intraventricular hemorrhage at the second planned interim analysis showed an increased rate of severe intraventricular hemorrhage or periventricular leukomalacia in the group given inhaled nitric oxide as compared with the placebo group (39 percent vs. 27 percent, P=0.02), but this difference was not significant at the conclusion of the trial. Severe intraventricular hemorrhage or periventricular leukomalacia as the cause of death was not significantly higher in the group given inhaled nitric oxide, although our trial was not adequately powered to address this question.

Post hoc analyses suggested hypotheses that deserve further study. Infants with a birth weight above 1000 g seemed to benefit from inhaled nitric oxide therapy, with a decrease in the incidence of death or bronchopulmonary dysplasia without any increase in the rate of intraventricular hemorrhage. In contrast, infants with a birth weight of 1000 g or less who were treated with inhaled nitric oxide had an apparent increase in mortality and a higher rate of intraventricular hemorrhage. Infants receiving inhaled nitric oxide by means of conventional mechanical ventilation also seemed to have higher rates of death than those receiving inhaled nitric oxide by means of high-frequency ventilation. The article by Mestan et al. in this issue of the *Journal*[31] documents improved neurodevelopmental outcome at 2 years of age in infants who received inhaled nitric oxide; neurodevelopmental follow-up at 18 to 22 months of age for the infants enrolled in our trial is in progress.

In conclusion, the use of inhaled nitric oxide in premature infants who had a birth weight of less than 1500 g and severe respiratory failure did not result in a decrease in the rate of death or bronchopulmonary dysplasia. The use of inhaled nitric oxide in premature infants born at less than 34 weeks of gestation should be confined to clinical trials until those who benefit can be identified.[32]

Supported by grants from the National Institute of Child Health and Human Development (U10 HD34216, U10 HD27853, U10 HD27871, U10 HD40461, U10 HD40689, U10 HD27856, U10 HD27904, U10 HD40498, U10 HD40521, U01 HD36790, U10 HD21385, U10 HD27880, U10 HD27851, and U10 HD 21373) and from the General Clinical Research Centers Program (M01 RR08084, M01 RR06022, M01 RR00750, M01 RR00070, M01 RR00039, and M01 RR00044).

Drs. Steinhorn and Ehrenkranz report having served as consultants to INO Therapeutics. Dr. Konduri reports having received grant support, and Drs. Finer and Van Meurs lecture fees, from INO Therapeutics.

We are indebted to Drs. William Benitz, Susan Hintz, and William Rhine for their advice and review of the manuscript.

APPENDIX

The following investigators participated in the Network Preemie Inhaled Nitric Oxide Study: Brown University Women & Infant's Hospital — W. Oh, A. Hensman, D. Gingras; Emory University, Grady Memorial Hospital — B.J. Stoll, L. Jain, E. Hale, I. Seabrook; Indiana University Riley Hospital for Children and Methodist Hospital — G. Sokol, D. Lorant, D.D. Appel, L. Miller, D. Chriscinske, J. Attwood; Northwestern University, Children's Memorial Hospital and Prentice — R. Steinhorn, M. Sautel; Stanford University Lucile Salter Packard Children's Hospital — K. Van Meurs, B. Ball, D. Proud; University of Alabama at Birmingham University Hospital — W.A. Carlo, S.S. Cosby, R.B. Johnson; University of Cincinnati University Hospital, Cincinnati Children's Hospital Medical Center and Good Samaritan — J. Fridriksson, B. Warner, M. Mersmann, B. Alexander, J. Shively, H. Mincey, M. Hoover, S. Sapienz, E. Stephenson; University of California–San Diego Medical Center and Sharp Mary Birch Hospital for Women — N.N. Finer, M.R. Rasmussen, C. Henderson, C. Demetrio, W. Rich, C. Joseph; University of Florida Wolfson Children's Hospital at Baptist Medical Center and Shands Jacksonville Medical Center — M. Hudak, S. Osbeck, E. Case, A. Kellum, L. Hogans; University of Rochester Golisano Children's Hospital at Strong — C.T. D'Angio, L. Reubens, G. Hutton; University of Texas–Dallas Parkland Hospital — A. Laptook, S. Madison, G. Hensley, N. Miller, G. Metoyer; University of Texas–

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Gordon, Valery (NIH/OD) [E]
Subject: RE: About SUPPORT
Date: Tuesday, April 23, 2013 4:46:00 PM
Attachments: Final elbw paper release.doc
Final Talking Points and QA.doc
Tyson, Outcomes, NEJM, 2008-04.pdf

Here is the web based outcomes tool paper, release and talking points.

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From: Gordon, Valery (NIH/OD) [E]
Sent: Tuesday, April 23, 2013 2:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: About SUPPORT

Thank you very much.

1. We want to write a paragraph that starts with: (b)(5)
(b)(5)

   We asked for a couple of examples, but I think that the request was insufficiently clear. We need a couple (or 3) examples of (b)(5)
(b)(5)

2. The next paragraph currently contains the following information: (b)(5)
(b)(5)

   I obtained this information from protocols, publications, editorials, and letters. But was there something significant about the 1950's? And what was meant by (b)(5)?

Does it mean (b)(5) Is there more (b)(5) And what happened after the 1950's? I found meta-analyses conducted between 2000 and 2009 (Cochrane Database Syst. Rev.). But surely something was done between 1950 and 2000?

These are the issues for which we need information at the moment.
If it is easier to talk with me on the phone, I provide my direct number below.

I appreciate your assistance with this project and your willingness to share your expertise.
Valery

Valery Gordon Ph.D., M.P.H.

Acting Director, Clinical Research Policy,

Office of Science Policy, OD

NIH

(301) 402-7667 (direct phone)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, April 23, 2013 2:16 PM
To: Gordon, Valery (NIH/OD) [E]
Subject: RE: About SUPPORT

That is fine.
Happy to try to answer any questions

Best regards
Rose

Rosemary D. Higgins, MD
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From: Gordon, Valery (NIH/OD) [E]
Sent: Tuesday, April 23, 2013 2:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: About SUPPORT

Hello Rosemary,
I don't think we've met, but I am part of the OSP team that is drafting an editorial for the NIH Director. The editorial is about research with pre-term infants and uses the SUPPORT study as an example of valuable research that has informed the care of these infants.
We have been working through Mona Rowe, who has obtained information from you and then passed it back to us. I can continue to use this pathway if this is best, or if it would be OK, I wonder if I can ask you a few questions that will help us to complete a draft of this document.
Would you please let me know?
Thank you,
Valery

Valery Gordon Ph.D., M.P.H.

Acting Director, Clinical Research Policy,

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NIH News
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Eunice Kennedy Shriver
National Institute of Child Health
and Human Development (NICHD)
http://www.nichd.nih.gov/

Hold For Release
Embargoed by Journal
April 16, 2008
5 p.m. Eastern Time

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NIH Study Reveals Factors That Influence Premature Infant Survival, Disability

Based on observations of more than 4,000 infants, researchers in an NIH newborn research network have identified several factors that influence an extremely low birth weight infant's chances for survival and disability. The findings offer new information to physicians and families considering the most appropriate treatment options for this category of infants.

Every day, physicians and new parents must struggle with the type of care to provide to extremely low birth weight infants, the smallest, most frail category of preterm infants. These infants are born in the 22nd through the 25th week of pregnancy—far earlier than the 40 weeks of a full term pregnancy. Many die soon after birth, despite the best attempts to save them, including the most sophisticated newborn intensive care available. Some survive and reach adulthood, relatively unaffected. The rest will experience some degree of life long disability, ranging from minor hearing loss to blindness, to cerebral palsy, to profound intellectual disability.

The study authors referred to the issue of providing intensive care for extremely low birth weight infants. For example, physicians and family members may be reluctant to expose an infant to painful life support procedures if the infant is unlikely to survive. In such cases, they may opt for "comfort care," which provides for an infant's basic needs, but foregoes painful medical procedures. In deciding the kind of care to provide, specialists at intensive care facilities traditionally have relied heavily on an infant's gestational age—the week of pregnancy a premature infant is born. Gestational age is known to play a large role in the infant's survival. For this reason, in many facilities, intensive care is likely to be routinely given to infants born in the 25th week of pregnancy, whereas infants born in the 22nd week may be more likely to receive comfort care.

The study authors noted, however, that it is often difficult to assess gestational age. Moreover, an estimate that is inaccurate by only a week could result in an infant receiving care that was not appropriate for his or her individual case. To identify other factors that influenced survival and disability risk, the study authors observed more than 4,000 extremely low birth weight infants in their network.

The researchers published their findings in the April 17 *New England Journal of Medicine*. In addition to gestational age, factors influencing survival and risk of disability consisted of: whether the baby is male or female (sex); birthweight; whether the baby was a single baby, or one of two or more infants born; and whether the baby's mother was given medication during pregnancy to prompt the development of the baby's lungs. Known as antenatal steroids, these drugs are typically given to women in premature labor, or who are at known risk for giving birth prematurely.

Physicians and parents may access an online tool that generates statistics, based on the factors the researchers listed in their article, at **http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/**. By specifying the baby's sex, weight, and information related to each of the variables listed above, physicians and family members can generate composite statistics on infant outcomes, based on the experiences of extremely low birthweight infants in the NICHD Neonatal Research Network study. The Web tool is not a substitute for a physician's careful assessment, but physicians and families may find the statistics it generates useful when considering the most appropriate care to provide an infant.

"Every individual is different, and no single tool can precisely predict a given baby's chances of survival or disability," said Duane Alexander, M.D., director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the NIH Institute that supports the Neonatal Research Network. "However, the researchers' findings, and the tool they developed, provide important information that physicians and family members can consult to help them make the most informed treatment decisions possible."

Additional funding for the study was provided by NIH's National Center for Research Resources.

The study involved only infants born at level III neonatal intensive care facilities. For this reason, the study findings may not apply to infants born at level I and level II facilities.

Level III facilities are the most advanced of neonatal care facilities. They offer the highly specialized medical care that extremely low birth weight infants need to survive. Most extremely low birth weight infants are born in level III facilities, as it is routine practice to rush women likely to give birth prematurely to level III facilities. However, in some cases, a woman may give birth before she can be brought to a level III facility. These infants are typically cared for at level I and II facilities until they are stable enough to transport to a level III facility.

To conduct their analysis, researchers in the NICHD Neonatal Research Network observed 4,446 infants born at 22-25 weeks' gestational age at hospitals around the United States, explained the NICHD co-author of the study, Rosemary Higgins, M.D., the program scientist for the NICHD Neonatal Research Network. Dr. Higgins explained that extremely low birthweight infants (those weighing less than 1,000 grams, or 2.2

pounds) make up about 1 percent of babies born in the United States each year, or roughly 40,000 babies a year.

Using standardized measures of mental development, vision, and hearing, the researchers assessed the health status of surviving infants when the infants were from 18 to 22 months corrected age—the age they would have been, had they been born full term. Dr. Higgins said that 49 percent of the infants in the study had died, 21 percent lived and did not have a disability, while the remainder experienced some degree of disability.

After conducting mathematical analyses of all the infants' cases, the researchers determined that infants were more likely to survive—and more likely to survive without disability—if they were of older gestational age, their mothers had been given corticosteroids, if they were female, were single born rather than part of a multiple birth, and been of a higher birthweight.

"Many neonatal intensive care units base treatment decisions mainly on gestational age," said Dr. Higgins. "We found that it's much more accurate if the assessment is based on the combination of 5 factors, rather than just on gestational age."

Dr. Higgins added that it is often difficult to accurately estimate gestational age, and a preterm infant may be as much as a week or two younger, or older, than believed.

She noted that the researchers found that race appeared to play no role in subsequent survival or chances of disability.

She stressed that the study data could not be used to predict with certainty the outcome of individual cases.

"A lot of medicine is a judgment call," Dr. Higgins said. "We provided our data in the hope that it would be helpful for making the best judgments for a particular situation."

A video interview with Dr. Higgins in which she provides additional information about the study and the online tool is available at http://www.nichd.nih.gov/news/resources/links/neonatal/.

# # #

The NICHD sponsors research on development, before and after birth; maternal, child, and family health; reproductive biology and population issues; and medical rehabilitation. For more information, visit the Institute's Web site at http://www.nichd.nih.gov/.

The National Institutes of Health (NIH) — *The Nation's Medical Research Agency* — includes 27 Institutes and Centers and is a component of the U. S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical, and translational medical research, and it investigates the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit *http://www.nih.gov*.

Essential points to get across:

1) the network conducted the study because more information is needed on the survivability of preterm infants
2) the study found that survivability was enhanced if the baby was female, was from a single birth (rather than a multiple birth) had a higher birth weight, and if the mother received steroids before the baby was born.
3) that these findings result from averages, may not necessarily apply to a particular case, and cannot substitute for a careful examination and history.
4) the Web form is only intended to inform treatment decisions, not predict what will happen.

Below are some potential answers to questions that reporters might pose.

Why did you conduct the study?

In our study, we looked at the most fragile of all preterm infants—those born at the 22nd through the 25th week of pregnancy. At birth, these babies weigh less than 1000 grams—that's about 2.2 pounds.

Caring for these babies in the neonatal intensive care unit is very difficult. Many will die, no matter what we do for them. Some will survive without any ill effects. The rest are in a vast gray area—they'll survive but with some degree of disability. And in many cases the disability will be profound: blindness, paralysis, deafness, or cerebral palsy. Some will be so disabled that they'll never be able to take care of themselves.

That's where the difficulty comes in. The vast majority of these babies can't breathe on their own, so they need a ventilator—that's a machine that pulses air into their lungs. They can't eat, so they need to be fed through a tiny plastic tube inserted into a blood vessel. They need to be monitored by a medical team around the clock.

If they think a baby is unlikely to benefit from intensive care, physicians and family members sometimes mutually decide to offer only comfort care, which provides for an infant's basic needs, but does not offer painful medical procedures. When people are making those kinds of difficult decisions, they need the best information possible.

Before our study, the only information that offered insight into a baby's chances was its gestational age—the week of pregnancy it was born. We knew that the closer a baby was to the 25th week, the better its chances. But it's often hard to calculate a baby's gestational age. It's easy to miscount by a week, and that could make a large difference in the baby's chances of survival.

We knew parents and physicians needed more information to go on. We tried to identify other factors that would give some idea of a baby's chances of survival or risk of disability. So we analyzed statistics on more than 4000 extremely low birth weight

infants in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

What did you find?

We found that, of the extremely low birth weight infants in our network, 27 percent survived without any ill effects to the brain and nervous system. We also found that certain factors—combined with the baby's gestational age—provided insight into how infants might fare. Survival—and survival without disability—was enhanced if the baby was female, was from a single birth (rather than a multiple birth) had a higher birth weight, and if the mother received steroids before the baby was born. These kinds of steroids force the baby's lungs to mature.

How can doctors and parents make use of the study results?

Our study provides what may be the largest source of information on the survival of extremely low birth weight infants. We're making it available to parents and physicians on the NICHD Web site (http://www.nichd.nih.gov). Doctors and parents can type certain key characteristics about a particular infant into a Web form. A program will provide statistics about survival and disability, based on the experiences of the 4000 infants in our network.

The Web form can be a useful reference for outcome data for a certain set of circumstances (whether the baby is male or female, gestational age, weight, single versus multiple pregnancy, and maternal steroids). This can provide information to families.

Can the study results be used to predict what will happen to an individual child?

The Web form isn't a crystal ball that will predict the future. Every baby is an individual human being and deciding what kind of care to provide is best done by the family and the health care team. There is no substitute for a physician's careful examination and evaluation. All decisions are a collaboration involving the physician's best judgment, while taking into account the family's wishes. However, our Web form will provide additional, reliable information to take into consideration when making difficult decisions about a baby's care.

Some reporters may come back to this last point, some more than once. In these cases, it may be helpful to rephrase the answer, to help crystallize the concepts involved—and underscore that the Web form is not proscriptive, but a tool to aid treatment decisions based on a broad array of other factors:

"All treatment decisions need to be made on a case by case basis."

"When parents and physicians are considering a baby's treatment options, multiple factors need to be considered, in addition to our statistics.

"No two cases are alike and every treatment decision must be individualized to that particular infant's situation and needs."

"Every case is slightly different."

"Each case has unique aspects, which must be taken into consideration."

"The overall health of infants in this age group can vary greatly. Judgment is needed for individual situations."

"The Web form is no substitute for sound medical judgment, taking into account the unique aspect of each patient's situation.

"Our statistics reflect the overall experience of infants who have been in our network, not the experience of an individual infant."

What are the responsibilities of physicians using the data on your form, under the Born Alive Infants Protection Act of 2001?

As I understand it, the act states that all infants who are alive—at any stage of development—at birth are considered to be human beings. I can tell you unequivocally that any infant born in our network [hospital, facility,] is regarded as a human being. We provide them with the most appropriate treatment for their individual cases. That's what we do for all our patients. All treatment decisions are a collaboration involving the physician's best judgment, while taking into consideration the family's wishes. Again, the data our Web form provides is only one source of information to be taken into account when considering the most appropriate treatment course for a particular infant.

Might statistics on the Web form be discouraging in some cases?

The Web form is only a part of the information that needs to be taken into consideration when deciding the most appropriate treatment options for an infant. There is no substitute for a physician's careful examination and evaluation. All decisions are a collaboration involving the physician's best judgment, while taking into account the family's wishes. However, our Web form will provide additional, reliable information to take into consideration when making the difficult decisions about a baby's care.

Could these data lead some parents to the conclusion that their infant might suffer severe disability and based on these data, make a decision not to continue medical support?

It's difficult to address hypothetical situations. Each situation is different. The Web form does not include treatment recommendations, only outcome data. The outcome data is just one factor in any decision regarding an infant's care. Also essential are a physician's careful assessment and evaluation of the infant, and taking the wishes of the family into account.

ORIGINAL ARTICLE

Intensive Care for Extreme Prematurity — Moving Beyond Gestational Age

Jon E. Tyson, M.D., M.P.H., Nehal A. Parikh, D.O., John Langer, M.S., Charles Green, Ph.D., and Rosemary D. Higgins, M.D., for the National Institute of Child Health and Human Development Neonatal Research Network*

ABSTRACT

BACKGROUND

Decisions regarding whether to administer intensive care to extremely premature infants are often based on gestational age alone. However, other factors also affect the prognosis for these patients.

METHODS

We prospectively studied a cohort of 4446 infants born at 22 to 25 weeks' gestation (determined on the basis of the best obstetrical estimate) in the Neonatal Research Network of the National Institute of Child Health and Human Development to relate risk factors assessable at or before birth to the likelihood of survival, survival without profound neurodevelopmental impairment, and survival without neurodevelopmental impairment at a corrected age of 18 to 22 months.

RESULTS

Among study infants, 3702 (83%) received intensive care in the form of mechanical ventilation. Among the 4192 study infants (94%) for whom outcomes were determined at 18 to 22 months, 49% died, 61% died or had profound impairment, and 73% died or had impairment. In multivariable analyses of infants who received intensive care, exposure to antenatal corticosteroids, female sex, singleton birth, and higher birth weight (per each 100-g increment) were each associated with reductions in the risk of death and the risk of death or profound or any neurodevelopmental impairment; these reductions were similar to those associated with a 1-week increase in gestational age. At the same estimated likelihood of a favorable outcome, girls were less likely than boys to receive intensive care. The outcomes for infants who underwent ventilation were better predicted with the use of the above factors than with use of gestational age alone.

CONCLUSIONS

The likelihood of a favorable outcome with intensive care can be better estimated by consideration of four factors in addition to gestational age: sex, exposure or nonexposure to antenatal corticosteroids, whether single or multiple birth, and birth weight. (ClinicalTrials.gov numbers, NCT00063063 and NCT00009633.)

From the University of Texas Medical School at Houston, Houston (J.E.T., N.A.P., C.G.); the Research Triangle Institute, Research Triangle Park, NC (J.L.); and the National Institute of Child Health and Human Development, Bethesda, MD (R.D.H.). Address reprint requests to Dr. Tyson at the Center for Clinical Research and Evidence-Based Medicine, University of Texas Medical School at Houston, MSB 2.106, 6431 Fannin St., Houston, TX 77030, or at jon.e.tyson@uth.tmc.edu.

*Members of the National Institute of Child Health and Human Development Neonatal Research Network are listed in the Appendix.

N Engl J Med 2008;358:1672-81.

DECISIONS TO INITIATE OR FORGO INtensive care for extremely premature infants are highly controversial.[1-7] In some centers, intensive care is provided to all very premature infants. In most centers, intensive care is provided selectively on the basis of specific gestational-age thresholds. Such care is likely to be routinely administered at 25 weeks' gestation but may be provided only with parental agreement at 23 to 24 weeks, and only "comfort care" may be given at 22 weeks. The evidence base providing support for these decisions is limited,[5,6] and the measurement error in assessing pregnancy length[8-13] may exceed the 1-to-2-week difference in gestational age that often prompts different treatment decisions.[2,3,5,7,14-16]

To facilitate more informed and better justified decisions, we assessed a large cohort of infants born at 22 to 25 weeks' gestation in the Neonatal Research Network of the National Institute of Child Health and Human Development to relate gestational age and other risk factors assessable at or before birth to the likelihood of death or adverse neurodevelopmental outcomes.

METHODS

ELIGIBILITY CRITERIA

We assessed infants born in 19 centers of the Neonatal Research Network at 22 to 25 completed weeks[17] of gestation (25 completed weeks are equivalent to 25 weeks 0 days to 25 weeks 6 days of postmenstrual age) between January 1, 1998, and December 31, 2003. We excluded infants with a major anomaly, a birth weight greater than 1000 g or the 97th percentile for gestational age (suggesting that the gestational age was underestimated[9,12]), or a birth weight of less than 401 g (below which few infants receive intensive care). Because we adopted the perspective of a physician deciding whether to initiate mechanical ventilation for infants considered very likely to die otherwise, we excluded the 31 infants who survived without mechanical ventilation (described below).

RISK FACTORS

We recorded the type of delivery, whether the birth was single or multiple, the child's sex, exposure or nonexposure to antenatal corticosteroid treatment within 7 days before delivery, race or ethnic group assigned by maternal report (black [not Hispanic], white [not Hispanic], Hispanic, or other), and birth weight. On the basis of previous findings,[13] the best obstetrical estimate based on the last menstrual period, early ultrasonographic examination, or other important prenatal findings was used to calculate gestational age, except in unusual circumstances when only an estimate by the pediatrician[18] was available. Details about the mother's menstrual history and ultrasonographic findings were not collected. We considered intensive care to have been provided if mechanical ventilation was initiated. (Nasal continuous positive airway pressure was unlikely to be administered or successfully used to avoid mechanical ventilation at 22 to 25 weeks' gestation.[19])

OUTCOME ASSESSMENTS

Research nurses using standardized definitions collected data before discharge. Standardized neurodevelopmental assessments were performed at a corrected age of 18 to 22 months by certified examiners trained in a 2-day hands-on workshop.[20] Neurodevelopmental impairment was defined as a score of 70 or below on either the Psychomotor Developmental Index or the Mental Developmental Index of the Bayley Scales of Infant Development, second edition (on a scale of 50 to 150, with 150 indicating the most advanced development), moderate or severe cerebral palsy,[20] bilateral blindness, or bilateral hearing loss requiring amplification. Profound impairment was defined as a Bayley score below 50 (untestable) or a level of 5 for gross motor function according to the modified criteria of Palisano et al.[21] (on a scale of 0 to 5, with 5 indicating that adult assistance is required to move).[20]

BENEFITS OF INTENSIVE CARE

We assessed the percentage of infants with the following prespecified primary outcomes: survival, survival without impairment, and survival without profound impairment. To avoid underestimating the potential benefits of intensive care, the maximum potential percentage of infants with favorable outcomes, had all infants received intensive care, was estimated. This estimation was calculated with the assumption that the percentage of infants with a potentially favorable outcome among those who had died without undergoing mechanical ventilation would be the same as the percentage of infants in the same risk category who had a favorable outcome and who underwent mechanical ventilation. Because infants who did not undergo ventilation tended

to be smaller, sicker, and less mature than infants in the same risk category who underwent ventilation (data not shown), this approach provides an optimistic estimate. This estimate can be considered the upper bound for the maximum potential percentage of study infants with a favorable outcome. These estimates were not intended to indicate the best outcomes achievable under ideal or future circumstances.

BURDENS OF INTENSIVE CARE

We divided the total number of hospital days or ventilator days before death or discharge home by the number of survivors in order to calculate an index of the infant distress, resource use, and costs[22] incurred per survivor. Similar calculations were performed to express the burdens of intensive care per survivor without profound impairment.

We estimated the number of additional hospital or ventilator days that would have been required if all study infants had been given intensive care, assuming that the additional survivors would require no fewer mean days per survivor than infants in the same risk category who were given intensive care. We regard this estimate as being conservative because the infants who died without receiving intensive care tended to be quite small and immature and might well have required more resources per survivor. The additional number of hospital or ventilator days per additional survivor without profound impairment was estimated in a similar manner.

STATISTICAL ANALYSIS

Each outcome for infants who received intensive care was analyzed with the use of a logistic mixed model[23,24] performed with the GLIMMIX procedure in SAS software, version 9.1.2 (SAS Institute). Gestational age, birth weight, sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple birth were selected a priori as predictor variables on the basis of previous studies of extremely premature infants.[6,25-27] Race or ethnic group as described above was unrelated to the three outcomes in bivariable and multivariable analyses and was not included. The type of delivery was also unrelated to death or to either impairment or profound impairment. The center entered the model as a random intercept to adjust for center differences while providing parameter estimates to permit center-free predictions.[21,22] Each completed week of gestation was entered as a categorical variable rather than a continuous variable because the latter resulted in inaccurate estimates of the outcome at 22 and 23 weeks' gestation. A comparison of observed parameter estimates with distributions derived from a bootstrap procedure involving 10,000 resamples provided support for the validity of the final model coefficients. For models of the three main outcomes, the variable estimates were within 0.4 to 2.3% of the median of the bootstrap estimates.

There were no significant interactions between gestational age and other risk factors. Data on infants not examined at 18 to 22 months were excluded from the denominator in analyses including neurodevelopmental impairment but were not excluded in analyses of death alone.

In assessing differences among centers, the expected proportion of infants who underwent ventilation with an adverse outcome was estimated for each center by applying our regression models to the population of infants who underwent ventilation in that center. The ratio of the observed to the expected rate was then calculated for each center.

To compare prognostic assessments based on multiple factors with those based on gestational age alone, we categorized all infants who underwent ventilation into 24 risk groups according to birth weight (≤25th, 26th to 75th, and >75th percentile for gestational age), sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple birth. For each group, the percentage of infants with an unfavorable outcome was predicted with the use of gestational age alone and according to gestational age, birth weight, sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple birth. The observed and estimated rates were then compared. No adjustment for multiple comparisons was performed. Two-sided P values of less than 0.05 were considered to indicate statistical significance. We used our models to develop a simple Web-based tool to estimate the likelihood of a favorable outcome.

RESULTS

The study population of 4446 patients is described in Table 1. The 31 relatively mature infants (0.7%) who were excluded because they survived without mechanical ventilation had a mean ges-

Table 1. Characteristics at Birth, Outcomes before Discharge, and Outcomes at a Corrected Age of 18 to 22 Months.*

Variable	All Infants (N=4446)	Infants Who Received Intensive Care (N=3702)	Infants Who Did Not Receive Intensive Care (N=744)
Characteristics at birth			
Prenatal care (%)	92	93	90†
Delivery by cesarean section (%)	42	48	9‡
Use of antenatal corticosteroids (%)	71	80	28‡
Race or ethnic group (%)†§			
Black	45	45	48
White	35	36	31
Hispanic	17	17	17
Singleton birth (%)	76	76	78
Female sex (%)	46	47	44
Gestational age (wk)	23.9±0.99	24.2±0.82	22.7±0.78‡
Birth weight (g)	648±124	670±118	536±84‡
Apgar score ≤3 (%)			
At 1 min	58	50	98‡
At 5 min	28	15	98‡
Predischarge outcomes			
Death (%)	49	38	100¶
Major morbidity (%)‖	50	60	NA¶
Death or major morbidity (%)‖	66	76	100¶
Median no. of ventilator days (5th–95th percentile)	19 (0–83)	26 (0–87)	0 (0–0)¶
Median no. of hospital days (5th–9th percentile)	72 (0–168)	88 (0–177)	0 (0–0)¶
Outcomes at 18–22 mo**			
Death (%)	49	42	100¶
Death or profound impairment (%)	61	53	100¶
Death or impairment (%)	73	67	100¶

* The study infants excluded 57 infants with a birth weight of more than 1000 g, 7 with ambiguous sex, 127 with major anomalies, 82 with a birth weight that exceeded the 97th percentile for gestational age, and 31 survivors who did not undergo mechanical ventilation. (The percentage of infants with each predischarge outcome was virtually identical for study infants and for all infants at 22 to 25 weeks of gestational age, including exclusions.) Plus–minus values are means ±SD. NA denotes not applicable.

† P<0.05 for infants given intensive care as compared with infants not given intensive care.

‡ P<0.001 for infants given intensive care as compared with infants not given intensive care.

§ Race or ethnic group was assigned by maternal report.

¶ The P value is not meaningful for this comparison.

‖ Major morbidity was defined as bronchopulmonary dysplasia requiring oxygen administration at 36 weeks' gestation, necrotizing enterocolitis requiring surgery, retinopathy of prematurity requiring laser therapy or surgery, grade III or IV intracranial hemorrhage, or white-matter injury detected on ultrasonographic examination.

** Outcomes were determined for 4165 infants, including 3421 who received intensive care. Data for infants not examined at 18 to 22 months were excluded from the denominator in analyses of death or profound impairment or death or impairment, but they were not excluded from analyses of death.

tational age of 24.7 weeks and a birth weight of 765 g; 68% were female; 87% were singletons; and 97% had received antenatal corticosteroids. At 18 to 22 months, none had died; 5 of the 27 examined (19%) had impairment, and none had profound impairment.

As expected, the study infants who did not receive intensive care differed from those who

received intensive care with respect to birth weight, gestational age, exposure or nonexposure to antenatal corticosteroids, and type of delivery (Table 1). The groups also differed with regard to race or ethnic group (P=0.04); the proportion of infants born at 22 and 23 weeks was highest in the centers with the largest population of black infants. No significant difference in race or ethnic group was present after adjustment for gestational age and center (P=0.74). Among infants who did not survive, the mean (±SD) age at death was 2.0±4.1 hours in the group of infants who did not receive intensive care and 22.4±45.2 days in the group of infants who did receive intensive care.

At 18 to 22 months, 49% of the study infants had died, 61% had died or had profound impairment, and 73% had died or had impairment. The rates for these outcomes according to the week of gestation were 95%, 98%, and 99%, respectively, among study infants born at 22 weeks; 74%, 84%, and 91% among study infants born at 23 weeks; 44%, 57%, and 72% among study infants born at 24 weeks; and 25%, 38%, and 54% among study infants born at 25 weeks.

PREDICTORS OF OUTCOME WITH INTENSIVE CARE

The benefit of a 1-week increase in gestational age varied somewhat at different weeks and for different outcomes (Table 2). In multivariable analyses, increased birth weight (per each 100-g increment), female sex, any use of antenatal corticosteroids, and singleton birth were each associated with reductions in risks of death and of death or profound or any neurodevelopmental impairment that were similar to the reductions associated with a 1-week increase in gestational age. (The regression equations relating these risk factors to outcomes are provided in Table A of the Supplementary Appendix, available with the full text of this article at www.nejm.org.)

Depending on these risk factors, the estimated probability of an adverse outcome with intensive care varied considerably among infants at the same gestational age (see Fig. A and B of the Supplementary Appendix). For example, among infants born midway between 24 and 25 completed weeks of gestation, the estimated likelihood of death or profound impairment was 33% for a 750-g, appropriate-for-gestational-age female singleton who received antenatal corticosteroids but 87% for a 525-g, small-for-gestational-age male

Table 2. Relation of Major Risk Factors to Observed Outcomes at a Corrected Age of 18 to 22 Months among Infants Who Underwent Mechanical Ventilation.*

Variable	Death		Death or Profound Impairment		Death or Impairment	
	Odds Ratio (95% CI)	Gestational-Age Equivalent Effect	Odds Ratio (95% CI)	Gestational-Age Equivalent Effect	Odds Ratio (95% CI)	Gestational-Age Equivalent Effect
Gestational age						
25 vs. 24 wk	0.62 (0.53–0.74)	1.00	0.66 (0.55–0.78)	1.00	0.70 (0.59–0.84)	1.00
24 vs. 23 wk	0.61 (0.52–0.73)	1.02	0.58 (0.46–0.73)	1.13	0.56 (0.42–0.74)	1.26
23 vs. 22 wk	0.54 (0.32–0.92)	1.15	0.50 (0.26–0.98)	1.31	0.56 (0.22–1.44)	1.25
Birth weight (per 100-g increase)	0.60 (0.55–0.65)	1.04	0.61 (0.56–0.66)	1.08	0.61 (0.56–0.66)	1.16
Female sex	0.64 (0.55–0.75)	0.97	0.55 (0.48–0.65)	1.19	0.48 (0.41–0.56)	1.47
Use of antenatal corticosteroids	0.55 (0.45–0.66)	1.14	0.54 (0.44–0.66)	1.23	0.53 (0.42–0.66)	1.33
Singleton birth	0.77 (0.65–0.92)	0.81	0.76 (0.64–0.91)	0.87	0.70 (0.58–0.85)	1.00

* The gestational-age equivalent effect indicates the reduction in risk for an adverse outcome with a particular risk factor relative to the reduction in risk with an increase in gestational age from 24 to 25 weeks (the reference group). The gestational-age equivalent risk for a given outcome is calculated by dividing the odds ratio for the reference group by the odds ratio for the factor of interest.

twin who did not receive antenatal corticosteroids.

Outcomes for infants who underwent ventilation varied among centers (P<0.001). Among centers that contributed data on 100 or more infants who underwent ventilation, the ratio of the observed to the expected rate of adverse outcomes ranged from 0.60 to 1.38 for death, 0.75 to 1.23 for death or profound impairment, and 0.85 to 1.17 for death or impairment.

USE OF INTENSIVE CARE AND INFANT RISK

As expected, the percentage of study infants who received intensive care increased progressively with increasing gestational age (from 23% at 22 weeks' gestation to 99% at 25 weeks' gestation) and birth weight (from 49% at 401 to 500 g to ≥97% at 701 to 1000 g). Intensive care was administered to more infants who received antenatal corticosteroids than to those who did not (94% vs. 58%). However, the percentage of infants who received intensive care was not significantly greater for singletons than for multiples (83% and 84%, respectively) or for female infants than for male infants (84% and 83%, respectively). This was also true at the lowest gestational ages (for female and male infants: 21% and 25%, respectively, at 22 weeks and 65% and 74%, respectively, at 23 weeks). For each major outcome, the percentage of infants who received intensive care was lower for female infants than male infants and for singletons than for multiples, after adjustment for the predicted likelihood of a favorable outcome with intensive care (P<0.01).

OUTCOME PREDICTION

The outcomes of the infant risk groups were predicted more accurately with the use of five factors (gestational age, birth weight, sex, exposure or nonexposure to antenatal corticosteroids, and single or multiple gestation) than with the use of gestational age alone, particularly for some subgroups (P<0.001 for the mean absolute difference between predicted and observed values and for the area under the receiver-operating-characteristic curve) (Table 3). (See Tables B and C of the Supplementary Appendix for specific subgroup data.)

BENEFITS OF INTENSIVE CARE FOR SMALL IMMATURE INFANTS

Even among the study infants at 24 weeks' gestation or less and with a birth weight of 600 g or less, outcomes varied considerably among different risk groups. The observed and maximum potential rates of survival without profound impairment were as low as 2 and 5%, respectively, for boys who weighed 401 to 500 g at 22 weeks' gestation and as high as 37 and 38%, respectively, for girls who weighed 501 to 600 g at 24 weeks' gestation (Fig. 1).

Table 3. Comparison of Models Using Gestational Age Alone with Models Using Five Factors.*

Outcome	Gestational-Age Model	Five-Factor Model	P Value
Death			
Mean absolute difference (%)†	11.9	2.8	<0.001
Range of values for observed minus estimated outcomes (%)†	−21 to 35	−11 to 16	NA
Area under the ROC curve (95% CI)‡	0.709 (0.692–0.726)	0.753 (0.737–0.769)	<0.001
Death or profound impairment			
Mean absolute difference (%)†	11.2	3.2	<0.001
Range of values for observed minus estimated outcomes (%)†	−27 to 30	−7 to 14	NA
Area under the ROC curve (95% CI)‡	0.704 (0.686–0.721)	0.751 (0.735–0.767)	<0.001

* The five factors are birth weight, gestational age, sex, exposure or nonexposure to antenatal corticosteroids, and singleton or multiple birth. NA denotes not applicable, and ROC receiver operating characteristic.

† The range of values for observed minus estimated percent differences are for 24 subgroup combinations of the five risk factors. P values were determined by chi-square analysis.

‡ The statistical comparison between the areas under the ROC curves is based on chi-square analysis, calculated with the use of a modified ROC macro in SAS software (SAS Institute). The ROC analysis indicates that the five-factor models were superior. Hosmer–Lemeshow goodness-of-fit tests derived from an equivalent fixed-effects model were not significant; these findings also provide support for the five-factor models.

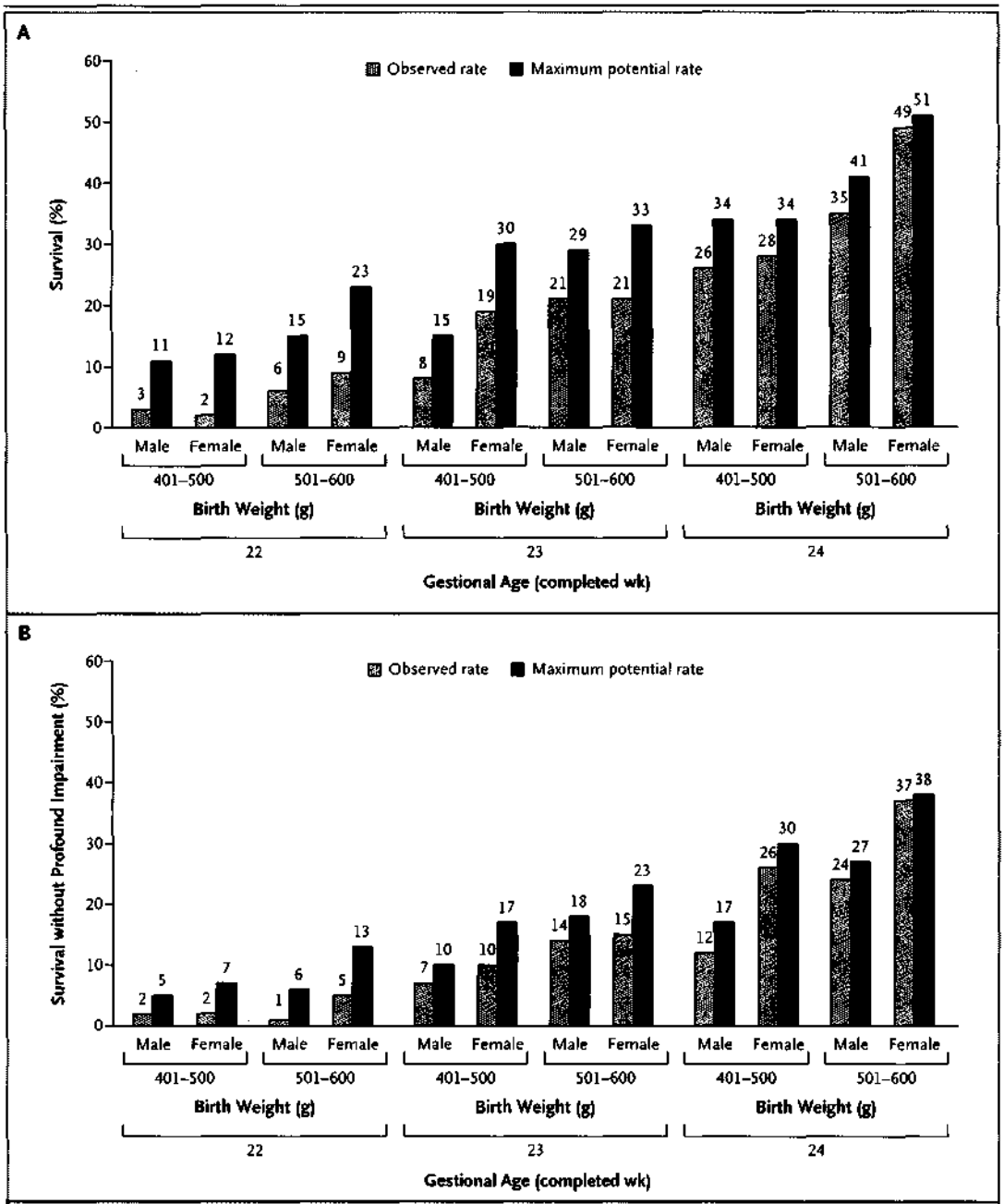

Figure 1. Observed and Maximum Potential Rates of Survival and Survival without Profound Impairment.

Panel A shows observed and maximum potential survival, and Panel B shows survival without profound impairment. Both rates are shown for an adjusted age of 18 to 22 months and calculated according to gestational age, sex, and birth weight for all of the smallest and most immature infants in the study.

BURDENS OF INTENSIVE CARE

Among all study infants, the total resource use per survivor and per survivor without profound impairment was high, particularly at the lowest gestational ages. The total resource use was consistently greater for male than for female infants (Table 4).

BENEFITS AND BURDENS OF UNIVERSAL INTENSIVE CARE FOR INFANTS AT 22 TO 23 WEEKS

We estimate that providing universal intensive care to all infants who were born at 22 to 23 weeks' gestation would have resulted in at least 1749 extra hospital days and 0 to 9 additional survivors per 100 infants treated. We estimate

that of 0 to 9 additional survivors per 100 infants treated, 0 to 5 would have survived without profound impairment and 0 to 3 would have survived without impairment.

DISCUSSION

Our findings challenge the widespread use of gestational-age thresholds alone in deciding whether to administer intensive care to extremely premature infants. In multivariable models of infants who received intensive care, female sex, exposure to antenatal corticosteroid therapy, singleton birth, and increased birth weight (per 100-g increment) were each associated with benefits similar to those of an increase in gestational age of approximately 1 week. In bivariable analyses as well as analyses adjusted for the center and the factors described above, race or ethnic group had no significant association with outcomes; these findings are similar to those in a previous Neonatal Research Network study.[25] At the same estimated likelihood of a favorable outcome, the likelihood of receiving intensive care was lower for girls than for boys and for singletons than for multiples. The likelihood of death or adverse developmental outcomes among different risk groups was more accurately estimated with the use of multiple risk factors than with the use of gestational age alone.

Outcomes are likely to be more closely related to gestational age in populations that virtually always undergo an early ultrasonographic assessment.[9,28] Estimates based on ultrasonographic examinations have been reported to have an error (±2 SD) of approximately 4 days at 12 to 14 weeks[29] and 7 days at 14 to 22 weeks.[30] However, even early estimates based on ultrasonographic examinations are subject to both systematic and random error,[10,31-33] and their accuracy has generally been assessed in relatively healthy populations evaluated by ultrasonographers who are aware of other indicators of pregnancy length. The error under field conditions at 20 to 30 weeks' gestation may be as great as 2 weeks.[14] For many extremely premature infants, the measurement error in assessing pregnancy length[8-14,29-31] is more than the 1-to-2-week difference in gestational age that would change treatment decisions with the use of current gestational-age thresholds. The error in estimating fetal weight should also be considered in antepartum counseling.

For multiple reasons, the effects of intensive care on extremely premature infants are unlikely to be determined in randomized trials. Observational studies are more subject to bias, particularly at the lowest gestational ages, when intensive care is used most selectively. Our study is also limited by the unavailability of data indicating how the obstetrical estimate of gestational age was assigned, the inability to determine the outcome for 6% of the study infants, and the use of center-based samples. A population-based study is needed to verify the absence of an important effect of race or ethnic group on the outcome for extremely premature infants. The better outcomes for infants who received antenatal corticosteroids result at least in part from their use when obstetricians are committed to optimizing outcomes.[34] Whether the use of corticosteroids has a benefit before 26 weeks' gestation remains to be determined in randomized trials.[35]

The strengths of our study include a prospective evaluation of a large, heterogeneous cohort and assessment of profound impairment, an outcome that some persons consider to be worse than death.[36,37] Total ventilator days or hospital days before discharge per infant with a favorable outcome were computed as indexes of cost, resource use, parental distress, and infant suffering due to painful procedures, prolonged intubation, and such complications as intracranial hemorrhage, necrotizing enterocolitis, and recur-

Table 4. Mean Resource Use per Survivor and per Survivor without Profound Impairment at a Corrected Age of 18 to 22 Months.

Resource Use	Gestational Age (wk)			
	22	23	24	25
Per survivor				
Total no. of ventilator days				
Male	119	88	63	43
Female	90	73	58	37
Total no. of hospital days				
Male	222	181	145	121
Female	168	163	136	111
Per survivor without profound impairment				
Total no. of ventilator days				
Male	266	135	85	53
Female	113	103	70	43
Total no. of hospital days				
Male	498	272	193	149
Female	206	231	164	127