

## **Task Force on Research Specific to Pregnant Women and Lactating Women Implementation Plan Meeting June 24, 2020**

On June 24, 2020, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC or the Task Force) convened a webinar to discuss its Implementation Plan. In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Interested individuals attended by registering in advance and viewing the meeting online by Webex.

Task Force members present:

- Diana Bianchi, M.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Chair
- Shelli Avenevoli, Ph.D., National Institute of Mental Health
- Karin Bok, Ph.D., M.S., National Institute of Allergy and Infectious Diseases (NIAID)
- Andrew Bremer, M.D., Ph.D., NICHD
- Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation
- Camille Fabiyi, Ph.D., M.P.H., Agency for Healthcare Research and Quality
- Dorothy Fink, M.D., Office on Women's Health, Department of Health and Human Services (HHS)
- Susan Givens, M.P.H., RN, March of Dimes
- Melissa Gorman, M.S.N., RN-BC, CCRN, Shriners Hospital for Children
- Elena Gorodetsky, M.D., Ph.D., Office of Research on Women's Health, NIH
- Bridgette Jones, M.D., University of Missouri, Kansas City
- Kristi Lengyel, M.B.A., UCB, Inc.
- Linda Lipson, M.A., Department of Veterans Affairs, retired
- Aaron Lopata, M.D., M.P.P., Health Resources and Services Administration
- Joan Nagel, M.D., M.P.H., National Center for Advancing Translational Sciences
- Voula Osganian, M.D., Sc.D., M.P.H., National Institute of Diabetes and Digestive and Kidney Diseases
- Victoria Pemberton, M.S., RNC, CCRC, National Heart, Lung, and Blood Institute
- Jeanna Piper, M.D., NIAID
- Jennita Reefhuis, Ph.D., Centers for Disease Control and Prevention
- Jeanne Sheffield, M.D., Johns Hopkins University
- Diane Spatz, Ph.D., University of Pennsylvania
- Robert Ternik, Ph.D., Eli Lilly and Company
- Kaveeta Vasisht, M.D., Pharm.D., Food and Drug Administration (FDA)

Executive Secretary Lisa Kaeser, J.D., NICHD, also was present.

Task Force members absent:

- Wendy Weber, M.D., Ph.D., M.P.H., National Center for Complementary and Integrative Health

Others present:

- NICHD staff members
- Members of the public

### **Welcome and Opening Remarks**

Dr. Bianchi began the meeting at 3 p.m. ET. The Task Force is working on an Implementation Plan to supplement its 2018 report to Congress and the HHS Secretary. That report included 15 detailed recommendations. The Implementation Plan offers actionable steps to implement the recommendations.

In August 2019, the Task Force formed working groups to develop steps to implement the recommendations. The Implementation Plan is now in its second draft. The goal for this meeting was to discuss and reach consensus on key questions and comments that remained outstanding on four of the recommendations and to discuss some overarching principles.

Dr. Bianchi reminded Task Force members that the recommendations have already been approved and were submitted in the September 2018 report. The purpose of this meeting was to reach consensus on the Implementation Plan.

Ms. Kaeser began a discussion of the outstanding issues related to the four recommendations.

### **Recommendation 7. Reduce liability to facilitate an evidence base for new therapeutic products that may be used by women who are, or may become, pregnant and by lactating women.**

Commenters said that there are substantial liability risks when including pregnant women and lactating women in research. Industry needs more and better incentives before they will become involved in this research. Ms. Kaeser posed the following questions to the Task Force:

- Are there incentives that would encourage industry to include pregnant women and lactating women in clinical trials despite liability concerns?
- Can the Task Force move ahead with these implementation steps even if the larger liability issues are unresolved?

### *Discussion*

Dr. Reefhuis said that if data about incentives are available, the Task Force should summarize it and suggest appropriate incentives. If the data are not available, the Task Force could suggest that another group explore that issue.

Dr. Ternik said that there are regulatory rules against incentivizing research in pregnant women and lactating women. The subgroup working on this recommendation concluded that the Task Force did not have the legal expertise to make a recommendation and suggested establishing an expert panel to explore liability and mitigation options. This suggestion is contained in Recommendation 7A.

Dr. Bucci-Rechtweg said that this recommendation refers to all *new* therapeutic products that may be used by pregnant women and lactating women, so it is important to understand what prevents industry from investing in new product development.

Ms. Kaeser said that the Task Force's charge is to encourage research. Should the recommendation be to encourage research on all new products that pregnant women or lactating women may take or on only the products that are already on the market?

Dr. Reefhuis said that pregnant women and lactating women should have access to as many new and existing products as possible, so the recommendation should be broad.

Dr. Spatz said that it is important to expand research to new therapeutics. For example, there is no FDA-approved medication to treat insufficient milk supply. Also, there may be different liability issues between pregnant women and lactating women.

Dr. Bucci-Rechtweg said that, overall, the Task Force should encourage research on the broad set of potential therapeutics. But given its focus on new therapeutics, this recommendation should encourage research on new products.

Dr. Reefhuis said that this research is complicated, so the Task Force should recommend convening experts who can make recommendations about this issue. Dr. Bremer suggested that, if the Task Force commissions a group to explore liability, it should produce separate recommendations for pregnant women and lactating women.

An attendee suggested putting a cap on liability for research studies.

Dr. Bucci-Rechtweg said that liability is the stumbling block to including pregnant women and lactating women in industry research. Addressing the liability issue to industry's satisfaction could encourage investment in all types of therapies.

Dr. Piper asked whether clinical trial insurance could help address the liability issues. Ms. Kaeser said that NICHD has used clinical trials insurance for some international trials, but requirements vary by country. Some countries require it before an institution can participate. This issue is worth exploring.

**Action Item:** Explore whether clinical trial insurance could help alleviate the liability issues that discourage industry from developing new drugs.

Dr. Bremer said that another possible industry incentive would be to provide longer patents or exclusivity rights to products whose development includes pregnant women and lactating women.

Dr. Vasisht said that products developed as part of the Best Pharmaceuticals for Children Act receive an exclusivity incentive. Although that incentive is not mentioned in Recommendation 7, it is mentioned in Recommendation 9.

Dr. Bianchi asked whether the entire recommendation needs legal review, or only parts of it. (There was no response to this question.)

Ms. Lengyel said that industry is the sector that researches new treatments, but the risk, reward, and liability must be resolved first.

Dr. Ternik said that liability and mitigation are addressed in Recommendation 7A. All of the sectors that do this research (e.g., industry, government, private and independent investigators) have liability risks, which is why the Task Force recommends consulting liability experts.

Dr. Ternik said that this recommendation covers pregnancy and lactation separately. It also applies to existing medications that pregnant women and lactating women may take and medications under development. The recommendation also breaks down medications into categories such as being on market and on patent or on market and off patent.

Dr. Ternik also said that Recommendation 7B addresses incentives, but incentives would not be effective unless liability were addressed. Many of the incentives suggested at this meeting are already written into the recommendation, but it would be a good idea to include the liability cap as an example.

An attendee asked whether having a pregnancy-specific indication for a drug could be an incentive. Dr. Bucci-Rechtweg said that it would depend on the type of drug. It could be an incentive if the therapy were new, but it would also depend on the life of the patent and how long the exclusivity would last. For an off-patent product, exclusivity would not be an incentive. If a drug is for pregnant women and lactating women only, then it would be its own indication, but those therapies are already being developed to treat those indications. She asked for the FDA representative to comment. Dr. Vasisht said that she will check on that and report back to the group.

**Action Item:** Dr. Vasisht will obtain further information on pregnancy- and lactation-specific indications.

An attendee said that liability is a balance between costs and the possible return. Dr. Bucci-Rechtweg said that the value calculation is a standard part of any indication evaluation for a drug. The drug company would look at the value calculation for the indication—in this case, for pregnancy- or lactation-specific indications. A value calculation can produce a positive, neutral, or negative valuation. The risk potential to a developing fetus can negatively affect the label, limiting the market for that therapy.

Dr. Piper said that Recommendation 7A recommends the creation of a panel to examine liability. The Task Force should suggest that Recommendation 7B include the formation of a group to evaluate incentives.

Dr. Avenevoli said that Recommendation 7A should describe the expertise that would be required of the expert panel on liability, and it should highlight the importance of Recommendation 7A over Recommendation 7B.

**Action Item:** NICHD will copy the chat that took place during the meeting and email it to the Task Force.

Dr. Vasisht said that the Hatch-Waxman Act may allow additional exclusivity for pregnant and lactation indications, just as it currently does for pediatric indications. Ms. Kaeser said that the suggestion will be considered.

**Recommendation 9. Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women.**

Ms. Kaeser posed the following questions to the Task Force:

- Some commenters suggested that the steps for this recommendation focus only on conditions specific to pregnancy and lactation, which would narrow the scope considerably. Does the Task Force agree?
- Are chronic conditions that pregnant women and lactating women have adequately covered in the other recommendations?

Dr. Lopata said that the recommendation should focus on therapeutics for any condition that can affect women who are of childbearing age. It should not be limited to pregnancy- or lactation-specific conditions. (But Dr. Lopata changed his mind in a statement below.)

Dr. Sheffield agreed, saying that most of the medications that she prescribes are for non-pregnancy-specific conditions, such as diabetes.

Ms. Lipson agreed, saying that the information about maternal morbidity and mortality and coronavirus disease 2019 (COVID-19) shows that a wide range of medications must be available, to include a range of conditions that pregnant or lactating women might have, although some medications may need to be phased in.

Dr. Bucci-Rechtweg said that she read the recommendation as referring only to new therapeutic products specific to pregnant and lactating women. Dr. Vasisht agreed that this recommendation seemed to be specific to conditions in pregnant women and lactating women. The other recommendations were written more broadly.

Dr. Piper recalled that this recommendation was written more narrowly to drive discovery for conditions specific to pregnancy and lactation, such as preterm labor, hyperemesis, low milk supply, and mastitis. The other recommendations were written to cover any condition that a pregnant or lactating woman could experience. Dr. Spatz agreed, saying that it is important to address the discovery needs in this recommendation.

Dr. Jones said that when reading the entire set of recommendations, it is clear that the Task Force is calling for broad research on therapeutics that pregnant and lactating women can use, but this

recommendation highlights the need for therapeutics for conditions specific to pregnancy and lactation.

Dr. Ternik said that lumping all therapeutics within this recommendation will diminish the specificity and focus it gives to new pregnancy- and lactation-specific therapeutics. Dr. Bremer said that this recommendation highlights an unmet need that might not be filled unless it is called out.

**Action Item:** Ms. Kaeser will ensure that the implementation of recommendations 9 and 9A focus on conditions related to pregnancy and lactation.

Ms. Kaeser asked whether the creation of a separate prioritization process for pregnant women and lactating women mentioned in Recommendation 9A should be limited to that recommendation.

Dr. Piper said that separate prioritizations are needed for conditions specific to pregnant women and lactating women versus for conditions that can affect any woman of childbearing age. Dr. Spatz agreed, saying that there is little research on lactation-specific conditions compared with pregnancy-specific conditions. Having a separate focus on lactation would help drive discovery. Dr. Ternik and Dr. Sheffield agreed.

**Recommendation 10. Implement a proactive approach to protocol development and study design to include pregnant and lactating women in clinical research.**

Ms. Kaeser reviewed the outstanding comments and questions related to this recommendation.

- Does the Task Force agree with comments discouraging the steps of a Task Force assessment and study plan, as recommended by the working group? (The alternative proposed is that sponsors should include pregnant women only if there were enough evidence to support inclusion.) What are the implications for industry? Are there other solutions to pursue?
- Some commenters made the case for pharmacokinetics (PK) and pharmacodynamics (PD) during the different phases of pregnancy and lactation. Are drugs metabolized differently throughout these periods? Are different drug formulations required?
- What other preclinical evidence is needed to provide information that would permit inclusion?
- How else can the safety of a drug be proved in the preclinical phase?

In terms of inclusion, Ms. Kaeser said that the original version of Recommendation 10A said that investigators must justify exclusion of pregnant women and lactating women in study designs. The proposed implementation step was to authorize FDA to require investigators and sponsors submitting new drug applications to submit a Task Force assessment and study plan.

Dr. Ternik said that the original version of Recommendation 10A assumed a level of infrastructure that does not exist. Dr. Bucci-Rechtweg said that the original intent of this recommendation was to require researchers who are writing a protocol to state why a population should be excluded. However, Recommendation 10A put in place a requirement for an entire

development program that does not fit with the original intent of the recommendation. The wording suggests that any time an investigator writes a protocol, FDA will require program development requirements. This wording is quite concerning.

Dr. Vasisht said that FDA would want an assessment or study plan and a plan to obtain safety and PK/PD data. Dr. Bucci-Rechtweg said that there would be discussion in the protocol about the population of inclusion and exclusion, but Recommendation 10A proposes a development plan for a pregnant or lactating population that would be submitted to the regulatory agency. Dr. Vasisht suggested rewording the recommendation.

Dr. Piper suggested moving the wording about the systematic plan from Recommendation 10A to Recommendation 10C, which talks in more detail about a systematic plan. The focus of Recommendation 10A was meant to be on the presumption of inclusion, with safety measures in place in case inclusion was not appropriate. Dr. Lopata said that the subgroup that worked on this was trying to mirror the pediatric plan. If it belongs in a different section or needs to be reworded, that is okay.

Dr. Bucci-Rechtweg said that this recommendation describes a procedure that is different than the one followed for pediatrics. Pediatrics is triggered at a milestone for the development program, not at the protocol submission. This recommendation was meant to stimulate inclusion of pregnant women and lactating women in research when it is indicated, but the recommendation has gone beyond that into a program development requirement in a pregnant or lactating population.

Ms. Kaeser asked how to demonstrate the shift of the presumption of exclusion of pregnant women and lactating women to the presumption of inclusion. Dr. Lopata said the intent was to demonstrate the shift to presumption of inclusion, not to create a new program. Dr. Reefhuis said that the group that wrote the recommendation meant to require investigators to justify exclusion, not create a new workflow. If rewording the recommendation would help, that could be done. Dr. Jones agreed and said that if the wording is too granular, it could be changed, but the recommendation should focus on inclusion. Dr. Bucci-Rechtweg said that Recommendation 10Cc goes beyond the original recommendation. Dr. Lopata suggested rewording the recommendation without losing the spirit of including pregnant women.

An attendee suggested that there is a need for novel research on an agent to treat milk supply and to understand the effect of agents on LGBTQ+ individuals who undergo transition and pursue pregnancy and lactation.

Dr. Piper said that the recommendation should also say that institutional review boards (IRBs) and FDA should consider the inclusion requirement in their protocol reviews. The IRBs and FDA will be the organizations that enforce this. Dr. Bucci-Rechtweg said that Recommendation 10D outlines steps for the IRBs.

Ms. Kaeser asked how the Task Force should describe the inclusion language. Is it a study plan? What could the Task Force call it?

Dr. Vasisht said that it would be a study plan. The presumption of exclusion of pregnant women and lactating women should be replaced with the presumption of inclusion. The process is like how pediatric research is reviewed. FDA works with industry on the development plans. FDA wants to get the data on this population in a safe and effective way.

Dr. Bucci-Rechtweg said that pediatrics research requires procedural steps, requirements for amendment, and multiple studies such as PK, preclinical, and efficacy and safety studies. This recommendation was not meant to require those studies. But the way this recommendation is written, it would require a full development plan. What data are available to support inclusion for a developing fetus? She recommended deleting Recommendation 10Cc. Ms. Kaeser said that she will consider Dr. Bucci-Rechtweg's suggestion as she prepares the next draft.

An attendee said that some COVID-19 studies are excluding pregnant women even if they probably should be included. FDA is asking that they be included.

Dr. Bucci-Rechtweg said that industry is facing the same challenge with pediatrics: Institutions are not allowing industry to include children. Recommendation 10Cc is about study design, but what is buried within the recommendation is an extensive Task Force plan for pregnancy.

An attendee said that a more comprehensive plan that could be considered at some point in development is needed. Ms. Kaeser said that she will discuss this with FDA representatives.

Dr. Lopata said that he and FDA staff would discuss Recommendation 10Cc outside of the meeting with Dr. Bucci-Rechtweg to be sure that FDA staff understand and can address her concerns.

Ms. Kaeser asked about the case for having PK/PD studies during different phases of pregnancy and lactation. Should that be called out in the implementation steps?

Dr. Bremer said that it should be. The biology and physiology of pregnancy is complex and changes at different phases of pregnancy. Early pregnancy is different from late-stage pregnancy. He suggested including the concept of pregnancy as a continuum.

Dr. Vasisht said that FDA already requires separate PK/PD data for the second and third trimester and postpartum.

Dr. Ternik said that the wording referring to drug formulations is concerning. He asked whether the intent was to discuss dosing as a function of pregnancy phase, not drug formulation. If it is drug formulation, he asked for examples of needing a different drug formulation.

**Action Item:** Ms. Kaeser will review the earlier documents for conflation of the concepts of drug formulation and drug dosing in this recommendation.

Dr. Piper said that absorption, elimination, and metabolism change throughout pregnancy, as well as pregnancy stage, must be considered during PK studies.

An attendee underscored the importance of inclusion in COVID-19 research. Pregnant women are at increased risk of severe infection.



Ms. Kaeser asked whether Task Force members had any further comments on the final two bullets regarding whether other preclinical evidence would be needed to permit inclusion of pregnant women and lactating women and whether there were other ways to test drug safety during the preclinical phase. There was no further discussion on these points.

An attendee suggested mentioning the inclusion of placental models in research, particularly for vaccine research.

**Recommendation 12. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women.**

Ms. Kaeser said that there are two areas that require further discussion.

- Are there other data sources we could cite?

Dr. Ternik said that the recommendations were skewed too heavily toward the evidence. (The rest of his comment was inaudible.)

**Action Item:** Ms. Kaeser will look at the original report and see whether there is more information there. Members who have examples should send them to Ms. Kaeser.

**Overarching Issues**

Within this section, the Task Force members discussed four issues that apply to multiple recommendations.

*Use of examples*

Ms. Kaeser asked whether there are too many examples within the recommendations, as some commenters have suggested.

Dr. Reefhuis said that including long lists of examples creates the impression that the list is comprehensive. She suggested limiting the number of examples, providing the same number of examples for each recommendation, and providing examples that demonstrate the range of concepts related to the recommendation. Dr. Bremer suggested adding that the examples are “including but are not limited to” those provided. Dr. Piper said that she preferred to have one or two examples per recommendation to clarify each recommendation’s intent.

An attendee asked whether NICHD networks such as the Maternal-Fetal Medicine Units Network will be available to do some of the research. Dr. Bianchi said that implementing these recommendations through the research agenda is an NICHD priority. The NICHD strategic plan acknowledges the lack of data in this area, and the development of drugs and devices for pregnant and lactating women is an area of focus. NICHD will use a variety of approaches to ensure the research goes forward. The networks have generated valuable evidence that has changed guidelines, but NICHD is looking at ways to improve the networks, and there are likely to be changes.

*Diversity of Study Populations*

Ms. Kaeser asked whether this topic is adequately addressed in the implementation steps.

Dr. Jones said that the topic is not adequately addressed, given the known disparities in maternal and infant morbidity and mortality and with COVID-19. This is an important opportunity to make sure that the research is inclusive and addresses continued health disparities. There are areas of the Implementation Plan where diversity can be called out specifically, not just in who is included in the research, but also in researcher training, the types of studies being supported, and what data are being produced that support the use of medications in certain populations. There should be more specifics in the recommendations of how to accomplish that. Ms. Lipson suggested making diversity and inclusion an overarching component.

**Action Item:** Ms. Kaeser will call out diversity in the recommendations. She will add an overall statement about diversity and inclusion. She will also include more diversity and inclusion language in training and will mention partner organizations, such as the National Medical Association and the National Hispanic Medical Association.

Dr. Spatz suggested including all healthcare providers, not just physicians.

An attendee said that there are ways to recruit people who are wary of research because of past injustices. Those ways should be mentioned. Another attendee said that the document should call out structural racism.

#### *Partnerships*

Dr. Bremer said that the partnerships with industry, regulatory agencies, and academia should be called out. Ms. Lengyel suggested calling out the role of the Foundation for the National Institutes of Health.

#### *Use of Registries*

Ms. Kaeser asked Task Force members to email their comments about whether the registries were adequately described in the document.

**Action Item:** Ms. Kaeser said that she would email Task Force members with the remaining questions.

**Action Item:** Ms. Kaeser will revise the Implementation Plan and return it to members by July 15. Members will review and return their comments by July 24. Ms. Kaeser will incorporate final comments and return the plan to members for concurrence. If an individual Task Force member disagrees with any part of the document, their dissent will be noted in the plan. The final Implementation Plan will be submitted to HHS Secretary Alex Azar, J.D., through NIH Director Francis Collins, M.D., Ph.D., on July 31.

Attendees should send additional comments to Ms. Kaeser at [kaeserl@mail.nih.gov](mailto:kaeserl@mail.nih.gov).

Dr. Bianchi thanked members of the Task Force for their work. The Task Force has “moved the needle” on this issue.