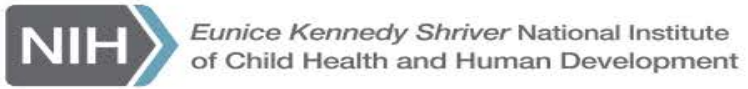
Task Force on Research Specific to Pregnant and Lactating Women

Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research



Major Points from Presentations

Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research

- Removing pregnant women as an example of a vulnerable population in the common rule *shifts to a presumption of inclusion*
- Investigators must justify exclusion in their study design
- The components of subpart B are useful to assess the risk ratio yet they are vague and burdensome for the investigator
- Investigators would benefit from best practices in interpretation; provide examples to allow them to cite an interpretation of risk

Lactating Women

- Given the importance of information on lactation on women and children
  - Investigators must justify exclusion of lactating women
  - Highlight the importance of this research including impact of not breastfeeding on mother and child
  - Lactation should be collected as part of study design

Reluctance to Include Pregnant and Lactating Women in Research

- Physiologic changes, patient complexity
- Liability / litigation
- Fetal risk inflation/distortion
- Limited knowledge regarding breastfeeding

Study Design

- Inclusion
  - Needs to be part of study design
  - If not included, further delay in research and information
  - Data needs to be usable
  - Appropriate outcomes required
- Numerous study designs available
  - PK/PD, observational, convenience, opportunistic studies all useful
  - Digital savvy participants – novel methods for research
  - Cannot solely use opportunistic data - false safety signals
  - Critical to also have randomized clinical trials
  - Need to compare to an approved therapy – however these are rare….
  - Studying the placenta is an opportunity that is not available to other fields
- Challenges
  - Time required for PK/PD studies; separation of mom/baby
  - Ideal to have a blood sample from baby for PK/PD
  - Funding
  - Baseline safety profile of therapies needed
  - Pooling data- data transparency, data accessibility, study design

Perspectives From the Trenches

- Funding: key issue
  - NIH main funder
  - Industry has limited funding support in obstetrics
  - Requires significant time to recruit, consent, etc
- Numerous burdens: regulatory, reliance on govt funding, limited researchers, paternalistic attitudes, limited expertise in IRB
- Limited pipeline of researchers
- Infrastructure is critical

Perspectives From the Trenches: Industry

- P&L universal exclusion aside from treatments specific for P&L
- Gap in skill-sets in industry; “condition of P&L”
- Chilling influence of liability – Key to address
- Decisions based on mechanism of action, benefit-risk analysis (including liability), timing in drug-development cycle, trial feasibility
- “Easy to say no”
- Proposal: concePTION with Innovative Medicine Initiative
- Able to engage with patients around their therapies, partnering with professional societies
- Scientific foundation is critical to decision for product development
- Open to incentives, need to understand the objective

Patient Perspectives: Research Benefits

- Altruism
- Additional testing, follow-up for child
- Knowledge of drug levels in breast milk
- Developmental assessments
- Cared for by experts

Stories are compelling

Major Points from Discussions

Methods to Alleviate/Alter Reluctance

- Incentives for participants, investigators
- Education regarding risk (include risk of lack of evidence)
- Education of importance of research – participant engagement
- Include P&L women in the “calls for research”
  - Eg Zika vaccine research did not include pregnant women
- Liability
  - Participating in research study
    - Injury compensation programs
  - Pregnancy and lactation specific liability
    - Long term outcomes
    - When does liability end (DES, thalidomide)
    - Industry/PI concern re long term litigation, class action lawsuit / disincentives
- Funding to support the extra effort required to provide risk-benefit ratio, consent time, etc

Additional Key Points

- Utilize public health crises to bring attention on priority areas
  - Opioids, Zika
- Leverage importance of opportunistic and intentional research
- Need to require plans for incident pregnancies on studies
  - Importance of gathering pregnancy outcome information
- Explore the incentives vs disincentives for research P&L women
- Capitalize on the momentum to increase intentional research and shift to inclusion of P&L women
- Study design type impacts: product development has specific guidance

Other Key Points

- Breast milk changes over feeding, as well as over time
- No evidence of transmission with incidental live vaccine exposure
- Milk banks and milk bank donors are an opportunity for research
- Pregnant minors often excluded
  - Regulations differ by state
- Consent process differs by state
  - Universal consent process? Harmonize across states?
- Issues related to inclusion of children/older populations similar
- Role of the payors
- Opportunity to utilize web to share stories of importance of research

Additional Discussion

- Given the long term outcomes needed, how to fund trials that last longer than 5 years – efficiency of doing trials
- Need to separate out in the report
  - Pregnant women and lactating women
  - Investigational drug development vs therapies in use
- Importance of developing public private partnerships to conduct first in human studies
- Review challenges in pediatrics of older drugs/orphan drug issues
- Need more purposeful studies in pregnancy
- Highlight knowledge gaps, where is most focus needed
- Product development vs products on the market
- Collective responsibility – industry, academia, progress needs to be made

Recommendations

Recommendation to Modify Subpart B

- Given the recognized autonomy of a pregnant woman,
- Given the evolution of family structure,
- Given that for a child only one parental signature is required for research to benefit the child (align with pediatric consenting),

46.204(e) in subpart B should be changed to maternal consent alone

Recommendation to Add Subpart D (46.406)

- Add in the option of “Minor increase over minimal risk”

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

Proposal

Additional Discussion - Proposal

- Create presumption of inclusion of pregnant/lactating women in clinical research
- Establish priority listing process (similar to NIH BPCA process)
- Identify categories of pregnant/lactating women to prioritize, e.g. Women already using drugs for particular conditions, create/utilize infrastructure to conduct trials in those populations first to establish expertise
- Extend to trials for new drugs