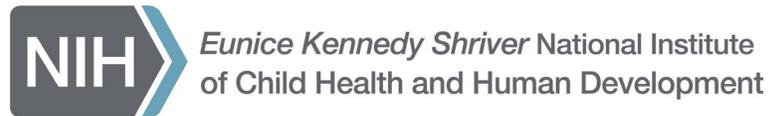


PRGLAC Working Group 2

Implementation Steps for Recommendations 1, 4, and 7





Recommendation 1

Include and integrate pregnant women and lactating women in the clinical research agenda

1A. Remove pregnant women as an example of a vulnerable population in the Common Rule

Progress:

- Pregnant women have been removed as an example of vulnerable population in the revised Common Rule. IRBs will now determine whether pregnant women are vulnerable and require additional protections.

Next steps:

- Consider developing educational approaches and revised guidance for IRBs (w/WG3), particularly regarding consent by pregnant women for participation in research
- Consider developing a document that provides strategies for designing ethical studies in pregnant and/or lactating women (w/ WG4)



1A. Remove pregnant women as an example of a vulnerable population in the Common Rule (cont.)

Stakeholders/federal agencies:

- Lead: OHRP
- All HHS operational divisions (e.g. NIH, CDC) that abide by the Common Rule
- Agencies/entities involved in educating IRBs



1B. The Food and Drug Administration (FDA) should harmonize with the Common Rule and remove pregnant women as a vulnerable population

Progress:

- A direct rule for FDA is already at the HHS/department level
- FDA is moving on a unified agenda (Office of Good Clinical Practice)

Stakeholders:

- Lead: FDA
- HHS



1C. The Department of Health and Human Services (HHS) should develop guidance to facilitate the conduct of research in pregnant women and lactating women

Progress:

- FDA has recently issued several guidance documents
- NICHD has a small obstetrics (OB) pharmacology research network

Next Steps:

- Review existing federal activities - 2018 PRGLAC summary – to identify gaps
- Review BPCA/PREA model for applicable elements
 - Begin with basic science, then move toward clinical testing
 - Is carrot/stick model applicable and feasible?



1C. The Department of Health and Human Services (HHS) should develop guidance to facilitate the conduct of research in pregnant women and lactating women

Next Steps (continued):

- Revise NIH inclusion policies to include these populations in research
- Re-educate IRBs on relevant issues – e.g., autonomy and consent
- Set expectations for collaborations across federal agencies and outside entities
- Consider an oversight committee/office at HHS to break down silos – model: IACC, or Vaccine Program office
- Revise post-market surveillance system to capture rare outcomes



1C. The Department of Health and Human Services (HHS) should develop guidance to facilitate the conduct of research in pregnant women and lactating women

Stakeholders:

- Lead: OWH/HHS for developing policy or hosting a standing group that would apply to all HHS operational divisions
- NIH
- FDA
- OHRP/HHS (policy guidance)



Take-aways for Recommendation 1

- Some of Recommendation 1 is complete or in progress.
- Need more information on the subset of studies that may require additional consent (sec. 204e) depending on whether there is direct benefit to the fetus v. benefit to the pregnant woman





Recommendation 4

Remove regulatory barriers to research in pregnant women

4A. Modify subpart B of the Common Rule

- change 46.204(e) in subpart B to maternal consent alone: Given the autonomy of a pregnant woman, the evolution of family structure, that for a child only one parental signature is required for research to benefit the child and to align with parental consent for pediatrics

- Add in the option of “Minor increase over minimal risk from subpart D to 36.046



4A. Modify subpart B of the Common Rule

Steps:

- Research the impact of 46.204 e as it stands
- Research the impact of adding “minor increase to minimal risk”
- Develop models of
 - drug concentrations in pregnant women (e.g. second and third trimester and postpartum),
 - partitioning of drug into breast milk;
 - drug concentrations in neonates and infants, incorporating evolving volume of breast milk intake, drug absorption, hepatic and renal clearance; and
 - relationship of drug concentration in neonates and infants to clinical effect.



4A. Modify subpart B of the Common Rule

Steps (continued):

- Collect data to inform proposed rulemaking, so that the revision(s) can be as narrowly focused as possible toward facilitating research
- If data shows that requiring only one consent for participation of a pregnant woman would increase knowledge about medications without increased risk to fetuses/infants, encourage implementation of this recommendation/ initiate proposed rulemaking by HHS/OHRP
- Consider gathering experts and stakeholders to define what minor increase over minimal risk might entail for a pregnant woman/fetus.
- Following these discussions, when consensus around definitions and impact has been built, support proposed rulemaking to modify subpart B.



4A. Modify subpart B of the Common Rule

Progress: None specifically focused on pregnant women/fetuses.

Stakeholders:

- Lead: OHRP for rulemaking, NIH/FDA for research
- For research: HHS/OHRP; NIH (e.g. NICHD's OPRU network); FDA; women's health organizations, pharmaceutical companies
- For model development:
 - Review ongoing efforts and coordinate globally - coordination with ConcePTION?
 - consider a consortium effort to pool available resources, such as the Health Environment Sciences Institute (HESI), the Critical Path Institute (cPath), or the IQ Consortium



4A. Modify subpart B of the Common Rule

Timeline:

- Rulemaking can be lengthy process: 7 yrs for latest revisions to the Common Rule; Pregnancy & Lactation Label Rule took 16 years
- Information collection, model development, consortium efforts: estimated 2-5 yrs



Take-aways for Recommendation 4

- Need the results of targeted research to inform a deliberative process regarding proposed rulemaking, in order to understand the ramifications of opening up the Common Rule/subpart B so that the resulting revision is not overly broad. Work with OHRP on how this would best be done.





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

7A. Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women
- Using the Vaccine Injury Compensation Program (VICP) as a model, however, include mitigation whether or not the therapeutic product achieves marketing approval



7A. Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women

Step 1

- Convene group with specific legal, regulatory, and policy expertise to develop a framework to address liability issues for research with pregnant and lactating women.
- Target a liability mitigation strategy to protect government-funded researchers who are working on therapeutics to be used by pregnant/lactating women
- Develop a matrix with relative liability for 1) currently on market but off patent therapeutics; 2) currently on market and on patent therapeutics; 3) new therapeutics under development (see matrix handout)
- Address requirements of federal and state informed consent regulations



7A. Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women

Step 2

- Until liability issues have been addressed, continue to define a research agenda that will inform the use of therapeutics by pregnant/lactating women.
- Continue preclinical studies for therapeutics in development to be used by pregnant/lactating women. Decisions refocused on whether *not* to include pregnant women.
- Prioritize research on therapeutics already on the market that are used for serious chronic conditions or emergency treatment in pregnant/lactating women
- Identify elements of the VICP program that might be applicable. Develop options for how such a program would be funded (e.g. a user fee for drugs already on the market that are used by pregnant/lactating women).
- Determine whether legislation would be required to establish such a program.



7A. Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women

Stakeholders:

- Lead: HHS
- For the legal analysis, a non-governmental convener, such as the National Academies of Sciences, Engineering and Medicine (NASEM)
- For the VICP model: HRSA/HHS and DOJ
- For prioritizing research on therapeutics already on the market: NIH
- For the toxicology/preclinical research: NIH, FDA, pharmaceutical companies, women's health organizations, consumer protection organizations



7A. Implement a liability-mitigation strategy for conducting research and evaluating new therapeutic products in pregnant women and lactating women

Estimated Timeline:

- A NASEM consensus study usually takes 18 months – 2 years.
- The NIH BPCA therapeutics prioritization process takes 1 year – 18 months.

Estimated Costs:

- A NASEM consensus study costs approximately \$1 - \$1.5 million
- Note that the VICP program (mandated by law) spends the interest on the capital of \$3 – 4 billion. In 2019, this came to \$230 million, including awards and attorneys' fees.
- The NIH portion of the BPCA program is capped by law at \$25 million annually.



7B. If liability mitigation is insufficient, consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data (such as pharmacologic and clinical data) on pregnant women and lactating women to inform dosing and safety



7B... consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data ...

Steps:

- Determine studies needed to inform dosing and safety of therapeutics used by pregnant and lactating women (PK/PD data).
- Examine BPCA program to determine whether data can be obtained from manufacturers (which may require incentives), or require government-funded studies (which may require congressional directives/funding).
- Consider a BPCA-like prioritization approach for classes of drugs, conditions experienced by pregnant/lactating women, and feasibility



7B... consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data ...

Steps (continued):

- Determine whether sufficient data can be obtained through postmarket studies; FDA may have to require but it does not have authority similar to that for pediatric studies mandated by the Pediatric Research Equity Act
- For NDAs or drugs recently approved, consider incentives to encourage testing
- For studies to obtain data from industry where incentives are insufficient, consider PREA mandatory approach
- Consider CDC's Treating for Two approach, which focuses on a risk-benefit analysis of drugs used for specific conditions
- Take best attributes of each of these programs and apply to therapeutics needed by pregnant/lactating women



7B... consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data ...

Stakeholders:

- Lead: FDA,
- FDA, NIH (fund studies to obtain data), pharma

Timeline:

- With appropriate resources, steps 1-4 could be accomplished on shorter timeframe (one year); steps 5-8 are longer term tasks



Take-aways for Recommendation 7

PRGLAC can't solve the entire liability issue for the U.S.

Information from the study of the mechanisms of teratogenicity would contribute to improved approaches to new drug development in order to minimize the risks of fetal malformation. Explore ways to increase the number of grants in this area of research and encourage non-federal efforts.





Discussion