Task Force on Research Specific to Pregnant and Lactating Women
Summary and Discussion of Work Products from Meetings 1,2,&3
Three-quarters complete!
Background

Familiar to many, but we may have some new participants
21st Century Cures Act

- Passed the House on November 30, 2016, by vote of 392-26
- Passed the Senate on December 5 by a vote of 94-5
- President signed the bill on December 13
SEC. 2041. TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN.

ESTABLISHMENT.—Not later than 90 days after the date of enactment of this Act, the Secretary of Health and Human Services (referred to in this section as the “Secretary”) shall establish a task force, in accordance with the Federal Advisory Committee Act...

(2) DUTIES.—The Task Force shall provide advice and guidance to the Secretary regarding Federal activities related to identifying and addressing gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities.
Task Force Implementation

- January 19, 2017
  - Authority delegated from HHS Secretary to NIH Director
  - NIH Director asks NICHD to lead
- February 2017
  - Task Force Plan submitted by NICHD
- March 13, 2017
  - Charter establishing Task Force filed
- May 2017
  - Slate of nominees prepared for Secretary’s approval
  - Federal members designated
Meetings

• Announced in Federal Register
• Each meeting has time dedicated to public presentations
• Open to the public
  • August 21-22, 2017
  • November 6-7, 2017
  • February 26-27, 2018
  • May 14-15, 2018
• Videocast and archived on the NIH videocast website
  • https://videocast.nih.gov/default.asp
Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC is tasked with identifying these gaps and will report its findings back to the Secretary.

Federal members include the directors of NIH, NICHD, the Centers for Disease Control and Prevention, the HHS Office on Women’s Health, and the HHS National Vaccine Program Office, as well as the Commissioner of Food and Drugs. Non-federal members include representatives from relevant medical societies, non-profit organizations, and industry.

Meetings
- August 21-22, 2017
- November 6-7, 2017
- February 26-27, 2018
- May 14-15, 2018

https://www.nichd.nih.gov/About/Advisory/PRGLAC
Important Deadlines

• June 30, 2018 finalized document to NIH

• September 2018 – Send report to HHS Secretary and Congress

• December 2018 – Secretary required to act on Task Force recommendations

• March 2019 – Task Force will sunset after two years unless extended
### Report Components and Strategy

| TF 4 | (5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women. |
| TF 1 | (4) Identification of Federal activities, including:  
(a) The state of research on pregnancy and lactation;  
(b) Recommendations for the coordination of, and collaboration on research related to pregnant women and lactating women;  
(c) Dissemination of research findings and information relevant to pregnant women and lactating women to providers and the public; and  
(d) Existing Federal efforts and programs to improve the scientific understanding of the health impacts on pregnant women, lactating women, and related birth and pediatric outcomes, including with respect to pharmacokinetics, pharmacodynamics, and toxicities; and |
| TF 3 | (3) Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women; |
| TF 2 | (2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research; |
| TF 3 | (1) A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies; |
Report – Draft Sections

• Executive Summary
• Introduction
• A plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of therapies
• Ethical Issues Surrounding the Inclusion of Pregnant Women and Lactating Women in Clinical Research
• Effective communication strategies with health care providers and the public on information relevant to pregnant women and lactating women
• Identification of federal activities
• Recommendations to Improve the Development of Safe and Effective Therapies For Pregnant Women and Lactating Women
• Appendices
Appendices

• Appendix I – Legislation
• Appendix II - Task Force Membership
• Appendix III - Meeting Agendas
• Appendix IV – Meeting Minutes
• Appendix V - Public Comments
• APPENDIX VI - Research on Therapies in Pregnant and Lactating Women
• APPENDIX VII - Federal Activities Related to Pregnancy and Lactation, by Agency
• Appendix VIII - Pregnancy Registries
• Appendix IX - Request for Information (RFI) and RFI Summary
• Appendix X – Historical Recommendations Regarding Testing of Therapies Used by Pregnant and Lactating Women
• Appendix XI - Lessons Learned from Implementing the Best Pharmaceuticals for Children Act (BPCA): Implications for PRGLAC
• Appendix XI - Common Rule Information
Executive Summary

• To be completed after May meeting
• High level overview with recommendations
Introduction, Background

- 21st Century Cures Act
- Establishment of the Task Force
- Knowledge gaps
Plan

• Objectives
• Research needs
• Collaborations
• Key considerations
• Assessing Progress and Outcomes
• Incentives and mitigation of liability
Ethical Issues

- Costs of exclusion without justification
- Balancing risks and benefits
- Research gaps
- Ethical issues
  - Presumption of inclusion
  - Consent
- Alternative study designs
- Industry considerations
Effective Communication Strategies With Providers and Public

- Case Study
  - Increase awareness
  - Engage influencers
  - Tailor the message
  - Evaluate
  - Partner for success

- Tactics for disseminating information to health care providers and to pregnant women and lactating women

- Offer continuing education
- Improve drug labeling
- Leverage the reach of professional societies
- Use traditional and non-traditional platforms
Federal Activities: Current Research

- Literature Analysis
- Results
- Key Research Gaps
- Funding Sources
Existing Federal Activities

- Research Activities
  - Prenatal Exposures
  - Safety and Efficacy of Medicinal Therapies in Pregnant and Lactating Women
  - Utilization and Quality of Care for Pregnant and Lactating Women
  - Health Care and Clinical Practice
- Communications
- Trans-Federal Collaborative Efforts

Summary Document
Recommendations to Improve the Development of Safe and Effective Therapeutics

• Focus of this meeting (May)
Appendix II: Task Force Membership

• Catherine Spong, Chair
• Lisa Kaeser, Executive Secretary
• Terry Adirim
• Shelli Avenevoli
• Diana Bianchi
• Karin Bok
• Andrew Bremer
• Christina Bucci-Rechtweg
• Camille Fabiyi
• Steven Foley
• Susan Givens
• Melissa Gorman
• Elena Gorodetsky
• Marjorie Jenkins
• Bridgette Jones
• Athena Kourtis
• Kristi Lengyel
• Linda Lipson
• Joan Nagel
• Victoria Pemberton
• Jeanna Piper
• Jeanne Sheffield
• Diane Spatz
• Robert Ternik
• Lois Tschetter
• Sayeedha Uddin
• Lee Wilson
Appendix V: Public Comments

Public Comments (oral and written)
August 2017
November 2017
February 2018
May 2018
Appendix VI: Research on Therapies in Pregnant and Lactating Women

Research on Therapies in Pregnant and Lactating Women

- Literature review: overall therapies
- Funding sources
- Specific conditions:
  - Literature
  - Current research activities
  - Research gaps

Categories for Analysis (Selected Conditions)
- Asthma
- Autoimmune diseases (excl diabetes)
- Cancer
- Central nervous system disorders
- Diabetes (all types)
- Endocrine disorders (excl diabetes)
- Hypertensive disorders
- Infectious diseases
- Low milk supply
- Mental health
- Pain
- Preterm birth
- Substance abuse
- Vaccines
Federal Activities Related to Pregnancy and Lactation, by Agency

- Agency for Healthcare Research and Quality (AHRQ)
- Centers for Disease Control and Prevention (CDC)
- Department of Agriculture (USDA)
- Department of Defense (DoD)
- Department of Veterans' Affairs (VA)
- Environmental Protection Agency (EPA)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)
- National Institutes of Health (NIH)
- National Vaccine Program Office (NVPO)
- Office of the Assistant Secretary for Health (OASH)
- Substance Abuse and Mental Health Services Administration (SAMHSA)
Appendix VIII
Pregnancy Registries

• Summary
  • 45 registries: 2/3 industry, ¼ non-profit
  • Majority by condition or medication
  • 46% Europe, 40% USA/Canada
  • Enrollment varies, most at 101-500

• Table of Registries
  • Name
  • Medicine(s)
  • Medical condition(s)
  • Organization/sponsor
  • Enrollment
  • Date established
  • Website
Appendix IX: Request for Information (RFI) and Summary

• NOT-HD-18-003: Request for Information
• Summary of responses
Appendix X: Historical Recommendations

- Historical Recommendations Regarding Testing of Therapies Used by Pregnant and Lactating Women
- Timeline: Meetings & Publications with Recommendations for Pregnant and/or Lactating Women
- Comparison of PRGLAC recommendations and historical recommendations
Appendix XI: Common Rule Information
Appendix XII: Federal Collaborative Activities
Feedback and Input

• Format
• Corrections / additions / suggestions?
• Anything missing?

Work in progress – finalized document to be submitted September 2018
Draft Summary Recommendations
From February Meeting
**Important Notes**

- These are *draft* based on discussions to date
- Aiming for reaction and refinement
- May meeting focused on recommendations
Workforce Recommendations

• Prioritize and support the development and training of pharmacologists and research scientists who understand pregnancy and lactation
• Prioritize and support the development and ob/gyn and pediatrics who understand pharmacology for studies in P&L
• Prioritize and support the development of investigators with obstetrical, lactation, and pharmacology expertise for industry, academics, and the federal workspace
• Facilitate a multidisciplinary approach to research teams including expertise in obstetrics, quantitative clinical pharmacology, clinical trial, behavioral/social sciences and regulatory sciences
Infrastructure Recommendations

- Leverage established networks to expand capacity and training.
- Provide support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, with rigorous methodology.
- Studies should account for the physiologic complexity throughout pregnancy and lactation. Note also that these may be impacted by other health conditions, environmental conditions, social determinants.
- Leverage advances in sampling techniques, bioanalytical techniques, multiplex assays, quantification of drug concentrations developed for work in pregnancy and lactation studies.
Incentives

• Funding for investigators to do this work
• Increasing feasibility of what needs to be done
• Disease specific registries
• Pregnancy:
  • Industry: reduce risk liability
    • Example vaccination compensation program
  • Clinician liability
  • Patent exclusivity (6 month extension) in peds – not likely to be a value in obstetrical studies –
    • has to be of public health benefit for children, needs to be completed and fairly respond to the written request
  • Written request for P&L is different between peds indications and P&L
    • Written request for pregnancy specific diseases
  • Liability concern is different for new entities vs drugs in use
• Do we need to get the label changed? Would this limit industry liability?

• Lactation
• Do we need to get the label changed? Would this limit industry liability?
Recommendations for Data

• Require studies to include plans for incident pregnancies to capture outcomes and add to available data.

• Develop requirements and provide support for disease focused registries with mandates that facilitate input of pertinent data with easy, transparent access to obtain information in real time.

• Recommend enhanced access and sharing of available data to provide information for pregnant and lactating women. Examples of available data include VA clinical database, DoD clinical database, federally funded studies, milk banks.

• Add P&L status to clinical trials, studies, data collections.
Recommendations to Increase Opportunities

• Encourage the use of numerous and innovative trial designs
• Facilitate longer award periods given needed duration for follow-up.
• Use PK/PD modeling and simulation to design protocols – identify dosage selection.
• Ensure trials are designed to appropriately capture the time dependency of physiologic changes in P&L, ideally having patients serving as own controls.
Recommendations to Increase Opportunities

• Develop scalable programs for evidence-based therapies
• Recommend use of new methods to do research and disseminate information – crowd sourcing, digital / internet
• Prioritize the development of new tools and methods to assay medications in breastmilk targeted to utilize small volumes and are sensitive to detect minute quantities
Regulatory/Legal and Policy Recommendations

- Rework the components of subpart B, although useful to assess the risk ratio they are vague and burdensome for the investigator

- 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

- Add in the option of “Minor increase over minimal risk” from subpart D to 36.046
Regulatory/Legal and Policy Recommendations

• Develop incentives to engage industry and agencies and to facilitate collaboration, development of public private partnerships. Develop incentives for drug development for both on and off patent therapeutics and P&L exclusivity incentives for drug sponsors.

• Create a regulatory framework for evaluating medication use in pregnant and lactating women.

• Limit the legal liability and ethical challenges for physician scientists, researchers, and industry for P&L research

• Create the presumption of inclusion of pregnant 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

• Require that lactation status be collected as part of every study design

• Facilitate the ability for investigators to work in P&L therapeutic studies; facilitate regulatory issues, funding, IRB review
Regulatory/Legal and Policy Recommendations

Need things to happen before can address these fully

- Recommend P&L studies to be performed for new molecular entities if relevant to the P&L communities
- Recommend that for all new product development, pregnant and lactating women should not be post-market evaluation
- Develop best practices in interpretation of benefit for investigators; provide examples to allow them to cite an interpretation benefit
- Develop best practices in interpretation of risk for investigators; provide examples to allow them to cite an interpretation of risk
Recommendations to Increase Awareness

• Highlight the importance of research on therapies in pregnancy and lactation including impact of not taking the medication during pregnancy and lactation as well as the impact of not breastfeeding on mother and child

• Develop evidence based tools for public to understand risk, evidence, and lack of evidence
Feedback and Input

• Format
• Corrections / additions / suggestions?
• Anything missing?

Work in progress – finalized document ~June 2018