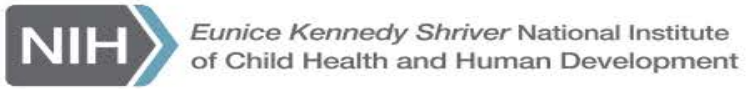
Task Force on Research Specific to Pregnant and Lactating Women

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.

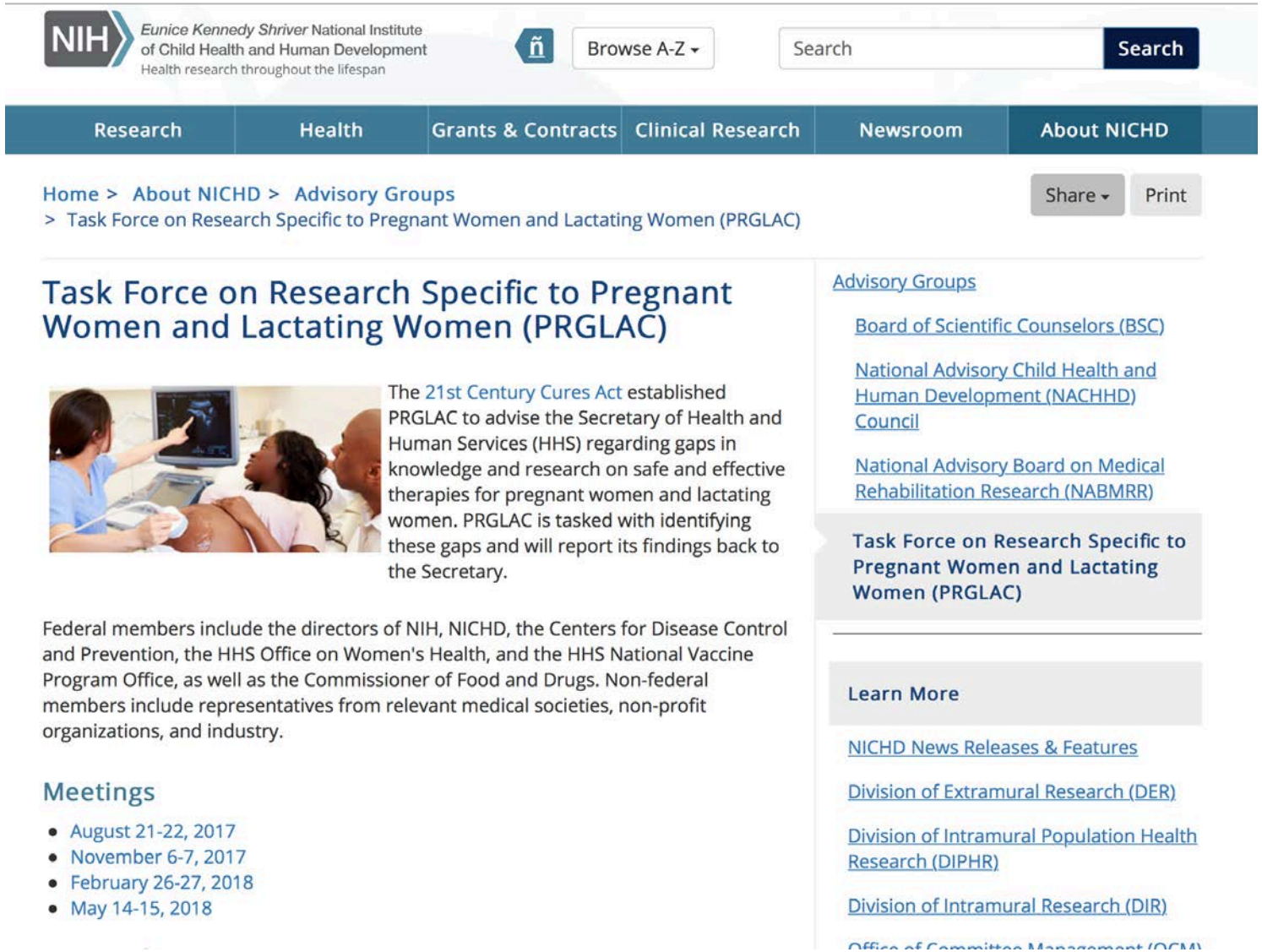
Task Force Implementation

- 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)



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 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;
TF 2	(2) Ethical issues surrounding the inclusion of pregnant women and lactating women in clinical research;
TF 3	(3) Effective communication strategies with health care providers and the public on information relevant to 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 provides 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 4	(5) Recommendations to improve the development of safe and effective therapies for pregnant women and lactating women.

Task Force Report
Draft

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

Appendix VIII: Research on Therapies in Pregnant and Lactating Women

To ensure that pregnant and lactating women and their children benefit from safe and effective therapies, many different types of research are necessary, and research projects of all types must be designed and implemented with the needs of pregnant and lactating women specifically in mind. Pre-clinical, fundamental research discoveries in biology, disease, and behavior are essential so that scientists can understand the underlying basis of a condition and identify potential therapeutic targets. Cell or tissue samples, animal models, and/or computer simulations are critical precursors to the design and testing of new approaches to diagnosis, prevention, and treatment. For pharmaceutical interventions, pharmacokinetics and pharmacodynamics (PK/PD) research -- the study of how drugs move through the body and the relationship between drug concentration and the resulting effect – are needed for developing safe and effective formulations and doses. Observational studies in humans – often through case series or cohort studies – shed light on the risk factors associated with a condition anddescribe prevention and treatment approaches used in the community. Epidemiological research can describe population trends in diseases or conditions and associated risk and resilience factors, giving scientists clues to improving human health. Randomized controlled clinical trials (RCTs) provide rigorous evidence that interventions are safe and effective for human use. Other types of research – such as studies of adherence and surveys to uncover variation in clinical practice – can help inform clinical decisions. Unfortunately, the pace of research progress across all types and methods has not been sufficient to ensure that pregnant and lactating women and their providers have enough scientific evidence for well-informed clinical decisions.

Objectives, Scope, Methodology, and Limitations

This analysis of published scientific evidence on therapies in pregnant and lactating women is based on research articles published over the last ten years. The analysis focuses on research in 15 selected categories, relating to conditions for which pregnant and lactating women are known to use medicinal therapies. (See Figure 1). For purposes of the analysis, medicinal therapies were defined to include drugs and vaccines, as well as vitamins, minerals, herbal remedies, and other supplements. The objectives were to supplement the expertise of the Task Force members by:

- Quantifying the research literature involving medicinal therapies for pregnant and lactating women, by category, topic, and research type;
- Identifying substantial research gaps, by category, topic, and research type; and
- Determining funding sources for the research, with a focus on identifying gaps and potential opportunities for collaborations.

Figure 1: Categories for Analysis (Selected Conditions)

- Asthma
- Autoimmune diseases (excluding diabetes)
- Cancer
- Central nervous system disorders
- Diabetes (all types)
- Endocrine disorders (excluding diabetes)
- Hyperemesis, nausea and vomiting
- Hypertensive disorders
- Infectious diseases
- Low milk supply
- Mental health
- Pain
- Preterm birth
- Substance abuse
- Vaccines

The analysis focuses on distinguishing and reporting the types of research, as opposed to judging the scientific merit or rigor of the design, implementation and conclusions of each published research project. The analysis provides information on the utilization of research approaches that can expand the scientific evidence base to inform clinical decisions about the use of therapies in pregnant and lactating women. "Original" research that systematically collects and reports new data, rather than describe individual cases or summarize previous findings, is most important to

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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)
- Hyperemesis, nausea and vomiting
- Hypertensive disorders
- Infectious diseases
- Low milk supply
- Mental health
- Pain
- Preterm birth
- Substance abuse
- Vaccines

Appendix VII: Federal Activities

Appendix VII: Federal Activities Related to Pregnancy and Lactation, by Agency

Introduction

An array of federal agencies support research, health care and clinical practice, communications, and collaborative efforts that are directly applicable to the HHS Task Force on Pregnant and Lactating women. Federal activities for 12 key agencies were identified by Task Force agencies, supplemented by systematic searches of agency databases, websites, and publications. These agencies include:

1. Agency for Healthcare Research and Quality (AHRQ)
2. Centers for Disease Control and Prevention (CDC)
3. Department of Agriculture (USDA)
4. Department of Defense (DoD)
5. Department of Veterans' Affairs (VA)
6. Environmental Protection Agency (EPA)
7. Food and Drug Administration (FDA)
8. Health Resources and Services Administration (HRSA)
9. National Institutes of Health (NIH)
10. National Vaccine Program Office (NVPO)
11. Office of the Assistant Secretary for Health (OASH)
12. Substance Abuse and Mental Health Services Administration (SAMHSA)

Agency Activities: Agency for Healthcare Research and Quality (AHRQ)

Research

A key part of AHRQ's mission is to invest in research to improve safety and quality of health care (https://www.ahrq.gov/research/ahrq-research.html). AHRQ supports extramural and intramural research related to pregnant and lactating women, often using large population-based and claims data. AHRQ also provides research resources, including health services databases, that can be used to develop evidence about utilization and effectiveness of treatments and quality of care.

AHRQ supports some studies specifically related to the safety and effectiveness of medications and therapies in pregnant and lactating women. These studies address a variety of conditions that are common in pregnant women. Some examples include:

- Researchers supported by AHRQ are combining previously collected data on the management of lupus during pregnancy to yield new information about optimal medication therapies to control lupus and improve pregnancy outcomes. In addition, researchers will be obtaining information from community rheumatologists to identify better ways to integrate expert recommendations for lupus management into medical practice.
- AHRQ supports multiple projects on the safety and effectiveness of antidepressants in pregnancy. One of these projects is using a large population-based Medicaid claims database to conduct a comparative effectiveness study, incorporating both maternal and fetal outcomes. A two-stage cohort study, using a large claims database, is designed to assess whether treatment of depression during pregnancy reduces the risk of postpartum depression.

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DRAFT

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

Appendix XII: Pregnancy Registries

Pregnancy exposure registries have been developed to collect health information on exposure to medical products (such as drugs and vaccines) during pregnancy. These databases can be helpful resources for researchers and regulatory agencies. Pregnancy registries were identified based on several sources: a listing provided by the FDA's Office of Women's Health[1], publications obtained through literature analysis, and web searches. A list of the pregnancy registries and large databases is provided below.

Summary

A total of 45 distinct registries were identified. As shown in Figure 1, about two-thirds were sponsored by industry and about one-quarter by nonprofit organizations. Although government organizations may be involved in providing expertise and in encouraging the establishment of registries, government organizations are typically not the sponsor or manager of registries. Several registries did not list a primary sponsor or responsible organization.

Figure 1: Pregnancy Registries, by Type of Sponsoring Organization

Registries may focus on a condition, medication, or both. As shown in Figure 2, most registries determine eligibility based on either medication or condition or both, but some restrict eligibility to only those women taking a specific medication.

Figure 2: Pregnancy Registries by Eligibility Criteria

[1] https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm

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

Appendix XIII: List of Acronyms

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

Draft Recommendations

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

Need liability dealt with for these

- 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

Discussion