Task Force on Research Specific to Pregnant Women and Lactating

Women Meeting

May 14 - 15, 2018

The Task Force on Research Specific to Pregnant Women and Lactating Women (Task Force or PRGLAC) convened the fourth of four two-day meetings on May 14 and 15, 2018, at the National Institutes of Health (NIH), 6710B Rockledge Drive, Bethesda, MD. In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Interested individuals could attend in person by registering in advance or by viewing the meeting online by NIH videocast. A video archive is available for Day 1 at: https://videocast.nih.gov/summary.asp?live=27386&bhcp=1 and for Day 2 at: https://videocast.nih.gov/summary.asp?live=27390&bhcp=1

Task Force members present:

- Catherine Spong, M.D. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Chair
- Shelli Avenevoli, Ph.D., National Institute of Mental Health (NIMH)
- Diana Bianchi, M.D., Director, NICHD
- Karin Bok, Ph.D., M.S., Department of Health and Human Services (HHS)
- Andrew Bremer, M.D., Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation
- Camille Fabiyi, Ph.D., Agency of Healthcare Research and Quality (AHRQ)
- Steven Foley, M.D., FACOG, Prowers Medical Center
- 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
- Marjorie Jenkins, M.D., M.Ed.H.P., Food and Drug Administration (FDA)
- Bridgette Jones, M.D., University of Missouri-Kansas City
- Athena Kourtis, M.D., Ph.D., Centers for Disease Control and Prevention (CDC)
- Kristi Lengyel, M.B.A., UCB, Inc.
- Linda Lipson, M.A., Department of Veterans Affairs (VA)
- Joan Nagel, M.D., M.P.H., National Center for Advancing Translational Sciences (NCATS)
- Victoria Pemberton, M.S., RNC, CCRC, National Heart, Lung, and Blood Institute (NHLBI)
- Jeanna Piper, M.D., National Institute of Allergy and Infectious Diseases (NIAID)
- Jeanne Sheffield, M.D., Johns Hopkins University
- Diane Spatz, Ph.D., University of Pennsylvania
- Robert Ternik, Ph.D., Eli Lilly and Company

- Sayeedha Uddin, M.D., M.P.H., HHS

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

Task Force members absent:

- Terry A. Adirim, M.D., MPH, Department of Defense (DoD)
- Susan Givens, RN, Mount Carmel St. Ann's
- Lois Tschetter, Ed.D., RN, IBCLC, South Dakota State University
- Lee Andrew Wilson, M.S., Health Resources and Services Administration (HRSA)

Review and Approval of Minutes

Dr. Catherine Spong welcomed the Task Force to its fourth meeting. The Task Force unanimously approved the minutes from the February 2018 meeting, after correcting the list of attendees to clarify Dr. Avenevoli was in attendance.

Summary and Discussion of Work Products from Meetings 1 - 3

Dr. Spong reviewed the legislative history behind the PRGLAC Task Force and reminded the group about pending deadlines. The Task Force report is due to the Secretary of HHS by September 2018 but must begin the clearance process by July 6, 2018. The Secretary has until December 2018 to decide whether and how to act on the PRGLAC recommendations. The Task Force's charter will expire in March 2019, unless the Secretary chooses to extend it.

Dr. Spong noted that the draft report was sent out to Task Force members for review, including all components of the report (covered in the first three meetings) except for the recommendations, which are the goal of this meeting. Task Force members made suggestions, and Dr. Spong requested that everyone with specific comments submit them by the end of the week.

Public Comment Period

Five members of the public provided comments for the Task Force members' consideration. These will be posted on the PRGLAC website.

Summary of Request for Information

Lisa Kaeser, J.D., NICHD, provided a summary of the responses to the Request for Information (RFI), which was open for public input between February and April 2018. The RFI received a robust response of 34 comments on a range of topics related to pregnancy and lactation.

Study design issues received the most comments, focusing on how to design studies that would include pregnant and/or lactating women (e.g., opportunistic studies), with some respondents stating that there should be a presumption of inclusion of pregnant and lactating women in research studies. While most concentrated on clinical studies and inclusion of these populations,

several also noted the need for basic research. Ethical issues also received attention, with most commenters stating that federal regulations should not continue to designate pregnant women as a "vulnerable" population. Eight of the submissions were similar, each calling for more research on therapeutics to address maternal milk supply. Respondents also called for better communication with pregnant and lactating women about research, recommending health care providers as a good avenue for sharing this information. Ten respondents mentioned that herbal supplements are widely used by pregnant and lactating women but have not been rigorously tested.

The full RFI summary will be posted on the PRGLAC website.

Task Force members continued discussion of the points raised by respondents to the RFI, particularly the study design and ethical issues posed by conducting research on therapeutics that include pregnant and lactating women. The point was raised that "inclusion" does not necessarily mean that every clinical trial includes these populations, but that their exclusion should be justified. However, if pregnant or lactating women will be key end users of a therapeutic, they should be included in the research unless fetal safety data have not been established. The suggestion was made to make federal regulatory requirements for pregnant women similar to those governing pediatric research.

FDA Presentation on Risk Communication Advisory Committee Meeting on the Pregnancy and Lactation Labeling Rule and new Guidance for Industry on Pregnant Women

Lynne Yao, M.D., FDA, updated Task Force members on FDA's new draft guidance for industry on pregnant women, which had been published after the last PRGLAC meeting. She reviewed the history of regulatory ethics requirements regarding participation of women of reproductive age in clinical studies. The new guidance discusses integration of pregnant women into clinical research, both in premarket and postmarket settings. It also covers the situation when a woman participating in a study becomes pregnant. The comment period on this draft closes June 8, 2018.

Dr. Yao also discussed the Pregnancy and Lactation Labeling Rule (PLLR), which is intended to provide health care providers with information to help with decision making related to pregnancy and lactation, who often have the responsibility to make those decisions in the absence of information, in conjunction with the end user. Task Force members continued their discussion of the ethical issues involved with conducting the studies needed to provide data specific to pregnant and lactating women, which will be the subject of many of the PRGLAC recommendations.

Review of Historical Recommendations in Pregnancy and Lactation

Elizabeth Wehr, J.D., NICHD, described her review of publications since the 1990s that made recommendations regarding the inclusion of pregnant women in research studies. More specifically, these recommendations covered research strategies, methods, topics, trial infrastructure, and resources. Over time, the recommendations have become increasingly

specific, such as the type of trials that would be feasible, the use of large databases, and emphasis on preclinical topics. Only recently has recognition of the need for research on lactation increased, which includes the impact of not breastfeeding if medications are being used. A number of these recommendations distinguished between research on new medications versus research on approved therapeutics in pregnant women.

Dr. Spong pointed out that the Task Force recommendations would be building on this earlier work. The need for tracking pregnant women's use of therapeutics through electronic health records was raised as one approach.

Open Discussion

Dr. Spong set the stage for the Task Force's discussions on its recommendations by reviewing the recommendations made during the first three meetings in several major categories, including expanding the workforce expert in this area, providing incentives to conduct research that includes pregnant and lactating women, data needs, optimal study designs, modifying regulatory or legal requirements, and increasing awareness and communications. Task Force members agreed that it is important to keep the number of recommendations manageable, to encourage action on them.

Incentives and Liability Discussion

A panel of experts, Christina Bucci-Rechtweg, M.D., Kristi Lengyel, MBA, Jeanne Sheffield, M.D., Robert Ternik, Ph.D., Kathleen Miller, Ph.D., Lynne Yao, M.D., and Karin Bok, Ph.D., M.S. (moderator) discussed potential approaches to reducing liability and creating incentives for industry to engage in research that includes pregnant and lactating women. Among existing programs (e.g., Orphan Drug Act, vaccine injury compensation program), the Best Pharmaceuticals for Children program (FDA, NIH), which provides incentives for industry to conduct research to inform pediatric drug labeling, was offered as a possible model, although several discussants cautioned against merging pregnant and lactating women into that program. The panel urged the Task Force to distinguish between incentives for testing drugs that are already on the market versus new drug development, to try to match incentives to address market failures (drugs to promote milk supply), and to recognize the need for foundational research. Resource limitations may require prioritization of the drugs to be studied. There is also a dearth of expertise that will require training in pharmacology related to obstetrics and lactation.

DISCUSSION: Recommendations to Improve the Development of Safe and Effective Therapies for Pregnant Women and Lactating Women

Dr. Spong outlined the plan for the Task Force's deliberations on PRGLAC's recommendations to the Secretary in its final report. The recommendations will be grouped and discussed according to the four major topic areas requested by Congress.

Dr. Avenevoli moderated the discussion on recommendations pertaining to the *development of a*

plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women. The Task Force was urged to recommend research that is conducted in a timely fashion. Another suggestion was to include metrics and/or timelines for each recommendation to be able to judge whether progress is being made. The group discussed how to identify the gaps in research, find funding for addressing those gaps, and how to prioritize which gaps need to be addressed first. Some discussants wanted the recommendations to be targeted toward preclinical and clinical research, while others emphasized the need for basic pharmacokinetic and pharmacodynamic research. To conduct this research, it was pointed out again that training programs in lactation and obstetric pharmacology need to be developed for health professionals.

Dr. Avenevoli also moderated the discussion on *ethical issues* surrounding the inclusion of pregnant women and lactating women in clinical research. Task Force members reached consensus on modifying subpart B of the Federal Regulations on the Protection of Human Subjects (Common Rule), changing the requirement for both maternal and paternal consent for participation of a pregnant woman in research to one of maternal consent alone (consistent with the requirement for pediatric research). The group also discussed adding an option of "minor increase over minimal risk" to subpart D 36.046, to help create a presumption of inclusion of pregnant and lactating women in research.

Dr. Piper moderated the discussion on the recommendations within the category of *effective communication strategies* with health care providers and the public on information relevant to pregnant women and lactating women. Task Force members commented on the idea of creating a public awareness campaign about the importance of pregnant and lactating women's participation in research, suggesting that health care providers and their professional organizations would be key conduits for the information. Such communications efforts should be evidence based. They also discussed tailoring the messages for different audiences and whether this could become a global effort.

Dr. Piper also moderated the discussion on *federal activities and the state of research*, coordination and collaboration on research, and dissemination of research findings. In addition to each federal participant agency's description of its activities relevant to pregnant and lactating women that will be included in the final report, Task Force members discussed how to leverage currently existing networks and collaborations to include more research and data collection on these populations, and to consider engaging in public-private partnerships. The group also discussed the role that industry registries could play, recommending that health care providers refer their patients for registry participation (prioritizing disease-focused registries) so that data on the effects of therapeutics can be gathered. Development of Common Data Elements would facilitate harmonization of these data. It was also noted that the new PregSource® research registry, sponsored by NICHD, would be adding a medications tracker as of September 2018.

Dr. Spong noted that Congress has asked whether the Task Force will recommend that it be extended.

Day 2

Recap and Goals for Day 2

Dr. Spong provided a recap of the previous day's discussions. She outlined some of the central points made during the earlier discussions, such as the need to address the issues around therapeutics used by lactating women separately from those used by pregnant women, and even women of reproductive age. The discussion on incentives and liability mitigation includes potential models to use for research on therapeutics used by pregnant and lactating women (BPCA, vaccine injury compensation). Regarding some of the ethical issues raised by research with these populations, both basic research and a change in culture may be required so that clinical research may proceed. By gathering evidence early (even in small studies), with the potential for following women to determine longer term outcomes, safety and efficacy data can be generated. However, there should also be a prioritization process, particularly at the beginning. Potential partners in this effort include agencies, industry, professional societies and nonprofit organizations.

Review of Recommendations with Voting

Dr. Spong reviewed the procedures for discussion, amendment, and voting on each of the PRGLAC recommendations. Ms. Kaeser recorded the votes on each of the following; each received a majority of votes:

1. **Include and integrate pregnant women and lactating women in the clinical research agenda**

    - Remove pregnant women as an example of a vulnerable population in the Common Rule
    - FDA should harmonize with the Common Rule and remove pregnant women as a vulnerable population
    - Develop HHS Guidance to facilitate the conduct of research in pregnant women and lactating women

2. **Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women**

    - Provide additional resources and funding for research to obtain clinically meaningful and relevant data for both specific and co-existing conditions in pregnant women and lactating women
      Including but not limited to:
        - Develop preclinical models
        - Expand basic science research to inform drug development
        - Develop new tools and methods to assay therapeutic products such as those that utilize small volumes and are sensitive to detect minute quantities including in human milk

- Develop new tools to assess pharmacodynamic response in pregnant women, lactating women, and children
- Fund clinically relevant research and studies to inform therapeutic product use in pregnant women and lactating women
- Design trials to capture long-term maternal, obstetric, and child outcomes

- Utilize longer award periods by government funders (beyond the typical 5-year award) when needed for study design and data collection

3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics

- Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
- Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science
- Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics

4. Remove regulatory barriers to research in pregnant women

- Modify subpart B of the Common Rule
  - Change 46.204(e) in subpart B to maternal consent alone
    - Given the recognized 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

5. Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women

- Highlight the importance of research on therapeutic products in pregnant women and lactating women, including the impact of not taking the medication during pregnancy and lactation as well as the impact of not breastfeeding on mother and child
- Engage stakeholders such as Department of Health and Human Services (HHS), professional societies, industry, advocacy groups, and public and global partners

6. Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women

- Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs

- Increase the engagement of health care providers to disseminate information from research findings to their patients
- Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries
- Develop appropriate strategies for sharing and interpreting research findings and risk

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**

    - 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
    - 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

8. **Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the National Institute of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model**

    - Provide specific funding
    - Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women

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

    - Create separate prioritization processes for pregnant women and lactating women
        - Unmet need examples in lactation: low milk supply, mastitis
        - Unmet need examples in pregnancy: preterm labor, hyperemesis
    - Consider a Biomedical Advanced Research and Development Authority (BARDA)-like model and the NIH vaccine model that takes clinical development up to Phase II

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

    - Investigators/sponsors must specifically justify exclusion in study design
    - Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation

- Develop a systematic plan on how data for pregnant women and lactating women will be obtained in a timely fashion to include pharmacokinetics/pharmacodynamics and safety
- Develop guidance for institutional review boards and investigators about the inclusion of pregnant women and lactating women in research
- Develop a systematic plan for if a woman becomes pregnant in a study to include whether product should continue, if un-blinding is necessary, how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information

11. Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women

- Provide financial support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, and methodologies.
- Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women
- Encourage networks/collaborations to engage in public-private partnerships to facilitate research

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

- Design health record systems to link mother and infant records
- Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries
- Use novel data resources
- Use innovative methods of data analytics
- Require common data elements to facilitate collaboration and use

13. Optimize registries for pregnancy and lactation

- Create a user-friendly website for registry listing
- Develop registry standards and common data elements that facilitate input of pertinent data with easy, transparent access to obtain information in real time
    - Include maternal, obstetric, and child outcomes, along with birth defects
- Facilitate access to data and transparency of information in registries
    - Use the ART registry as a model
- Develop disease/condition-focused registries
    - Move toward a single registry for all therapeutic products with input from stakeholders

14. **The Department of Health and Human Services Secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019**

15. **Establish an Advisory Committee to monitor and report on implementation of recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical research**

Adjournment

Dr. Spong said that the draft PRGLAC report would be sent to the Task Force members for final review prior to its submission for clearance at the end of June 2018. The final report will be sent to the Secretary, HHS, and to Congress, in September 2018.

After thanking the Task Force members and participants for their hard work, Dr. Spong adjourned the meeting.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

Lisa Kaeser, J.D.
Executive Secretary, Task Force on Research Specific to Pregnant Women and Lactating Women