TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN IMPLEMENTATION WORKING GROUP OF COUNCIL

Report on Implementation Progress

July 2024

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Contents

Introduction

Background

More than 90% of women[1] take at least one medication during pregnancy and lactation.[2] However, pregnant women and lactating women are often excluded from clinical research. Their exclusion from research is motivated in part by concerns about the possibility of medication use harming the developing fetus during pregnancy or breastfed child during lactation. Less attention is given to the potential harms of untreated disease for both the woman and the fetus or child, which can be significant.

As a result, pregnant women, lactating women, and their health care providers must make decisions about whether to discontinue treatment for preexisting conditions or initiate treatment for emerging medical conditions without adequate scientific knowledge of the safety and efficacy of these treatments during pregnancy or lactation. In many cases, the scientific evidence does not exist or is insufficient to inform on the safe or efficacious use of a medicine. Because of this, pregnant women and lactating women often receive conflicting information about medication use.

Pregnant women and lactating women should not be protected from research; they should be protected through research. Evidence-based answers are required for women and their clinicians to make fully informed choices based on the risks and benefits—as they apply to the mother, her fetus or child, and the breastfeeding child—of medicating or not medicating conditions during pregnancy and lactation.

Recognizing the urgent public health problem and ethical concerns posed by the lack of data on safety and dosing of medications during pregnancy and lactation and the longstanding obstacles to inclusion of pregnant women and lactating women in clinical studies, the U.S. Congress passed legislation in 2016 to establish the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). Its goal is to identify gaps and propose recommendations to overcome the obstacles.

The PRGLAC Recommendations and Implementation Plan

PRGLAC was established by the 21st Century Cures Act (P.L. 114-255) to advise the secretary of Health and Human Services (HHS) on activities related to identifying and addressing gaps in knowledge and research on safe and effective therapies for pregnant women and lactating

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[1] The Working Group acknowledges that not all individuals who can get pregnant identify as women, and that inclusion of gender minority individuals in pregnancy and lactation research is critical. However, we have opted to use language that mirrors the original PRGLAC report and implementation plan. Additionally, most of the scientific literature and other publications in this area focus on cisgender women; we therefore use the term *women* to encompass a broader group of individuals who have the capacity to become pregnant or lactate.

[2] 2018 PRGLAC Report, Section 6: Appendix VI. https://www.nichd.nih.gov/about/advisory/PRGLAC

women. Recognizing that the scope needed to be defined, the Task Force discussed the meaning of the term *therapy* in the wording of the mandate and voted at its first meeting to focus on drugs, vaccines, and dietary supplements because of their widespread use by pregnant women and lactating women.

Based on the information gathered through four open meetings and a public comment period, the Task Force developed a report that included 15 recommendations to improve the inclusion of pregnant women and lactating women in clinical research. The Task Force submitted its report to the HHS secretary in September 2018.[3]

PRGLAC Recommendations

- Recommendation 1: Include and integrate pregnant women and lactating women in the clinical research agenda.
- Recommendation 2: Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women.
- Recommendation 3: Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics.
- Recommendation 4: Remove regulatory barriers to research in pregnant women.
- Recommendation 5: Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women.
- Recommendation 6: Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women.
- 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.
- Recommendation 8: Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women, using the National Institutes of Health (NIH) Best Pharmaceuticals for Children Act (BPCA) as a model.
- Recommendation 9: Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women.
- Recommendation 10: Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research.
- Recommendation 11: Leverage established infrastructures/collaborations and support new ones to perform research in pregnant women and lactating women.
- Recommendation 12: Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women.
- Recommendation 13: Optimize registries for pregnancy and lactation.
- Recommendation 14: The HHS secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires, in March 2019.

[3] https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations

- Recommendation 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.

In addition to the 15 recommendations outlined above, PRGLAC acknowledged several larger barriers to advancing research with pregnant or lactating women. Most notably, Task Force members emphasized that "the culture of protecting pregnant women and lactating women from research has proven resistant to change," and that progress will require not only concrete actions but also cultural shifts.

PRGLAC Implementation Plan

In March 2019, the HHS secretary formally extended PRGLAC's charter to March 2021. For this extension, the Task Force was charged with providing further guidance on the implementation of the recommendations made in its 2018 report.

The Task Force met four times during the extended charter period to develop an implementation plan composed of feasible and actionable steps that could make realistic progress toward ensuring that pregnant women and lactating women are more comprehensively and appropriately included in research. The draft implementation plan was based on discussions held by four working groups of the Task Force, prepared worksheets, presentations made during in-person meetings, and public comments. It was then further reviewed and discussed by the entire Task Force. Finally, the PRGLAC Implementation Plan was submitted to the HHS secretary in August 2020.[4]

Congressional Mandate and Formation of the Working Group

The Fiscal Year 2023 Consolidated Appropriations Act (P.L. 117-328) included funding and language for HHS to create an advisory committee to monitor and report on the implementation of the PRGLAC recommendations. An accompanying U.S. House of Representatives report (House Report 117-403) charged the HHS secretary with submitting a report to Congress—within 180 days of the act's enactment date—that outlined the progress of the implementation of all 15 recommendations detailed in the 2020 PRGLAC Implementation Plan.

In 2023, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) formed the PRGLAC Implementation Working Group of Council[5] (the WG)—a subgroup of NICHD's National Advisory Child Health and Human Development (NACHHD) Council—to take on this task. The focus of the WG is not to develop new recommendations but to track the implementation of the original 15 recommendations, identify barriers to implementation, and provide suggestions to facilitate implementation.

The WG has members affiliated with federal entities, including the Centers for Disease Control and Prevention (CDC), NIH, and the U.S. Food and Drug Administration (FDA). The WG also

[4] https://www.nichd.nih.gov/about/advisory/PRGLAC

[5] https://www.nichd.nih.gov/about/advisory/council/PRGLAC-implementation-WG-of-council

has members who represent specialty organizations, such as March of Dimes, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal–Fetal Medicine (SMFM). Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals, and Susan Abdel-Rahman, Pharm.D., Health Data Synthesis Institute, served as co-chairs. A full list of the WG members appears in Appendix I.

Information Gathering

The co-chairs and NICHD staff met before the WG meetings to deliberate on the entities that ostensibly served as owners of or major contributors to each recommendation. They also identified relevant representatives who could brief the WG on completed, in-progress, and planned activities. In 2023 and 2024, the WG convened three meetings to hear presentations from government agency officials, professional society representatives, advocates, and other interested parties. The goal of these sessions was for the WG to understand the implementation status of each recommendation. WG members were instructed to consider presentations made during these sessions as "representative but not necessarily fully comprehensive" of all ongoing or planned actions for the recommendations whose status were being evaluated. To facilitate discussion at these meetings, the recommendations were grouped under five thematic topics:

- Cluster A: Conduct of clinical research and trials
- Cluster B: Education, outreach, training, and career development
- Cluster C: Policy, regulatory issues, and liability
- Cluster D: Registries and real-world data (RWD)
- Cluster E: Novel drug discovery and development

Following each public meeting, the WG characterized the progress made toward implementation of the PRGLAC recommendations. To do this, WG members utilized the results and initiatives described by invited speakers from federal agencies and nonfederal entities at these meetings, the review of publicly available materials pertaining to implementation progress, and discussion of the knowledge brought by WG members from their related work sectors. Appendix II lists the details and agenda of each meeting. A summary of the sessions is included in Appendix III.

It should be acknowledged that the time constraints imposed on the WG process and the lack of visibility into all ongoing initiatives precluded a comprehensive review of all possible activities relevant to recommendation implementation. Accordingly, the WG made its determinations based on the information that could be assembled and shared in the time frame allotted.

In June 2024, the WG presented its findings and recommendations to the NACHHD Council, and the council voted to approve the WG's report.

Implementation Updates

This report provides the WG assessment of progress made to date on each of the recommendations in the 2018 PRGLAC Report. The WG was not tasked with providing new recommendations to promote the inclusion of pregnant women and lactating women in research. Rather, the goal of the WG was to assess the degree to which the original recommendations have been implemented, provide suggestions to aid in their execution where applicable, note major barriers that may derail a recommendation, and identify any other relevant stakeholders who are essential to securing successful implementation of the PRGLAC recommendations.

Based on the road map outlined in the 2020 PRGLAC Implementation Plan, the WG examined progress toward the individual implementation steps proposed in the 2020 plan to determine which recommendations:

- Are implemented
- Are in progress or planned
- Have not been implemented and may be in need of attention, resources, or reconsideration

To consider a recommendation implemented would require that all actions needed for implementation were completed or nearly completed. Given the abbreviated time frame since the implementation plan was released, only a few recommendations are expected to be implemented at the time of this report. Many of the recommendations are highly complex and still in the planning stages, or in progress. As certain policy recommendations may take years to be realized, many in-progress recommendations are showing progress toward their goal but need more time to be evaluated. Highly complex recommendations and/or those with multiple process owners are more likely to be in progress. Additionally, some recommendations contain elements that may require congressional action (e.g., legislative reform, appropriations). To achieve what was intended in the original PRGLAC plan, these will require additional time to implement once they are adequately supported.

Implementation Progress

Although every attempt has been made to reflect the current landscape of activities related to implementation of the PRGLAC recommendations, the following sections should not be construed as a comprehensive inventory of activities and initiatives.

Implementation Progress: Recommendation 1

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.

1B. FDA should harmonize with the Common Rule and remove pregnant women as a vulnerable population.

1C. HHS should develop guidance to facilitate the conduct of research in pregnant women and lactating women.

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

Status: Implemented

Recommendation 1A, which is relevant only to pregnancy, was fulfilled in January 2019 with revisions implemented into the Code of Federal Regulations (CFR) for the protection of human subjects in research. In particular, the update to HHS regulations in 45 CFR 46, subpart A,[6] known as the Common Rule, included the removal of pregnant individuals as an example of a vulnerable population that requires additional ethical scrutiny before participating in research.

According to the HHS Office for Human Research Protections (OHRP), institutional review boards (IRBs) are therefore responsible for determining whether pregnant women require added protections or should not participate in a specific research protocol. However, many IRBs have not yet modernized their review criteria sufficiently to incorporate pregnant women in research, reducing the degree to which Recommendation 1A has been operationalized.

[6] https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html

Recommendation 1B: FDA should harmonize with the Common Rule and remove pregnant women as a vulnerable population.

Status: In progress

Implementation of Recommendation 1B, which is relevant only to pregnancy, is in progress. FDA has an ongoing effort to harmonize with the Common Rule (45 CFR 46, subpart A) through revisions to its regulations for the protection of human subjects (21 CFR 50) and for the review process of IRBs (21 CFR 56). These two FDA regulations are nearly identical to the Common Rule, with a few exceptions. FDA has drafted the proposed rule, which is expected to be finalized by the end of 2024. The WG underscored the importance of finalizing this guidance.

Recommendation 1C: HHS should develop guidance to facilitate the conduct of research in pregnant women and lactating women.

Status: Not implemented

Recommendation 1C has not yet been implemented. Per the written update OHRP sent to the WG on March 2024, OHRP has not published guidance to help inform and facilitate the inclusion of pregnant women and lactating women in clinical trials.

1C.a. Determine which studies may require additional consent.

Per 45 CFR 46.204(e), which applies to federally funded research, for a pregnant woman to participate in clinical studies in which there is the prospect of direct benefit solely to the fetus, additional consent from the father is required (see Recommendation 4). More information continues to be needed on the extent to which additional consent is protective for these studies.

1C.b. Review existing resources to inform guidance.

OHRP charged the Secretary's Advisory Committee on Human Research Protections (SACHRP) to consider the topic of justice as it relates to 45 CFR 46. In its 2021 recommendations, SACHRP points to the problematic historical exclusion of pregnant individuals and other populations from research.[7]

1C.c. Review federal program experiences to determine successful approaches.

This step has been implemented. There is a need to develop programs that provide industry incentives and clinical research infrastructure to evaluate products in pregnant women and lactating women (see Recommendation 8 and Recommendation 9).

[7] https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-consideration-of-the-principle-of-justice-45-cfr-46.html

1C.d. Consider expanding post-market surveillance to capture rare outcomes.

This step does not require additional attention, because the existing post-market surveillance system is structured to capture all reportable outcomes, including rare ones.

1C.e. Consider how the HHS guidance could facilitate research.

The 2021 recommendations from SACHRP also include relevant considerations for IRBs, such as a recommendation that IRBs should look closely at—and require strong justification for—proposals that would exclude certain groups. SACHRP's recommendations are a resource for the regulated community. However, they do not constitute OHRP guidance.

1C.f. Consider using a central IRB.

Implementation of this step does not require additional development. Use of a central versus local IRB is a standard consideration for researchers.

1C.g. Provide education and oversight.

This step has not been implemented. However, SACHRP is charged with reviewing ongoing OHRP efforts and other HHS activities directed toward protections for human subjects in research, with particular emphasis on several populations, including pregnant women.

Implementation Progress: Recommendation 2

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

2A. Provide additional resources and funding for research to obtain clinically meaningful and relevant data for specific and co-occurring conditions in pregnant women and lactating women.

2B. Utilize longer award periods by government funders (beyond the typical 5-year award), when needed, for study design and data collection.

Recommendation 2A: Provide additional resources and funding for research to obtain clinically meaningful and relevant data for specific and co-occurring conditions in pregnant women and lactating women.

Status: In progress

Significant progress has been made toward implementation of Recommendation 2A.

2A.a. Develop a more systematic approach to funding and enhancing research.

NICHD has established several clinical trial networks for the improvement of maternal, fetal, and infant outcomes, including the Maternal–Fetal Medicine Units (MFMU) Network, the Neonatal Research Network (NRN), and the Global Network for Women's and Children's Health Research (the Global Network). These networks have recently been modified to expand funding opportunities for clinical trials and observational studies that involve pregnancy and lactation and to leverage existing infrastructure with the addition of a data coordinating center. The new structure should allow for more multisite studies and cross-network collaborations, with enhanced sharing of biospecimens and increased therapeutic information from clinical trials (see Recommendation 10). Another national resource of note is the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub, designed to accelerate therapeutics-focused research in obstetrics, lactation, and pediatrics; synergize with other resources and networks; and support data availability. The Sentinel System, a key component of the Sentinel Initiative, includes mother- and infant-linked data used to study pregnancy, fetal, and infant outcomes. Additionally, CDC funds post-market surveillance and research relevant to therapeutics used during pregnancy and lactation.

2A.b. Prioritize the research.

There are ongoing efforts to prioritize research needs in specific therapeutics for pregnant women, lactating women, and postpartum women (see Recommendation 8 and Recommendation 9). Although there has been some progress, dedicated funding is needed to ensure that robust and modernized nonclinical safety methods are developed and utilized for research that can help de-risk clinical studies. Investing in basic science focused on safety of

therapeutics is especially important, because much of the hesitancy about using medications during pregnancy and lactation is due to safety concerns.

2A.c. Expand the availability of preclinical models.

In January 2024, NIH approved the concept of a Common Fund research program, the Complement Animal Research In Experimentation (Complement-ARIE) program, to catalyze the development, standardization, validation, and use of human-based new approach methodologies.[8] The Complement-ARIE program hosted a challenge competition to crowdsource new methodologies to model human biology. Several of the winners of the Complement-ARIE challenge winners developed methodologies and products that could be used to model drug interactions during pregnancy.

The Complement-ARIE trans-agency working group is engaging with the Foundation for the National Institutes of Health (FNIH) and other foundations and institutes to transform the nonclinical space, including for reproductive studies. As NIH increases its investment in the Complement-ARIE program, there may be an opportunity to expand research efforts into novel nonclinical models for pregnancy and lactation. It is possible that these models could be used earlier in the drug discovery phase to identify and eliminate properties in therapeutics that are harmful in pregnancy (see Recommendation 7, Recommendation 9, and Recommendation 10).

2A.d. Maximize the usability of data.

Efforts are ongoing to increase the availability and utility of data, for example, through the NICHD Data and Specimen Hub (DASH)—a centralized, cloud-based repository that allows researchers to share and solicit de-identified data and biospecimens from clinical studies funded by NICHD.[9] DASH is constantly being upgraded and modernized.

The MPRINT Hub contributes to enhancing data use in therapeutics research through many of its components and collaborations. The MPRINT Knowledgebase and Portal Core[10] extracts usable information related to maternal and pediatric therapeutics and incorporates it into a broader ontological framework that can be mapped to various types of data, such as electronic health records (EHRs) and drug ontologies. The MPRINT Real-world Evidence Core uses mother–baby linkages to improve the characterization of maternal and pediatric drugs by combining EHR data with biospecimens and other types of data (see Recommendation 12).

FDA's efforts to support data resources include work through the Advancing Real-World Evidence Program and the Sentinel Initiative (see Recommendation 2A.a).

[8] https://commonfund.nih.gov/complementarie

[9] https://dash.nichd.nih.gov

[10] https://mprint.org/research/scientific-cores/kb-portal.html

2A.e. Develop new research tools.

NICHD uses Notices of Funding Opportunities (NOFOs) to promote the development of novel generalizable tools and algorithms. Examples include machine learning model systems with multi-omic and clinical data, *in silico* models that use RWD, tools using pharmacoepidemiologic data, and artificial intelligence (AI) tools for data extraction, harmonization, and interoperability (see Recommendation 12).

In the newly formed Complement-ARIE program, representatives from multiple agencies and the pharmaceutical industry will provide input on developing human-relevant translational models and ways to use the data to inform decision making. This program could explore complex *in vivo* or *ex vivo* type models, complex cellular constructs, and methods for assessing drug transport, metabolism, and kinetics across the placental barrier.

FNIH has also supported working with private partners to understand disease pathways and discover new targets and biomarkers. Work is ongoing to leverage data science and partnerships for disease insights, biomarkers, and drug targets (see Recommendation 11).

Recommendation 2B: Utilize longer award periods by government funders (beyond the typical 5-year award), when needed, for study design and data collection.

Status: Implemented

Recommendation 2B has been implemented, with three NICHD networks—the MFMU Network, the NRN, and the Global Network—now using 7-year award periods. The most recent funding cycle for these awards spans 2023 to 2030, and there is a desire to extend this longer award time to other networks in the future. Developing a map of the existing networks could incentivize collaborations across sites by providing additional resources to accelerate research initiatives for pregnancy and lactation.

However, the extended award periods implemented in networks have not been accompanied by similar shifts in other components of the infrastructure. For example, the funding extension does not apply to all NIH or other federally funded pregnancy-focused studies. Additionally, although networks are funded for 7 years, individual studies within the networks are funded for 5 years. Flexibility is still needed in other research mechanisms to allow for longer terms to accommodate trials that recruit enough pregnant women and lactating women to generate the data necessary to inform changes to clinical practice.

Implementation Progress: Recommendation 3

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

3A. Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science.

3B. Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science.

3C. Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics.

The challenges and opportunities identified for obstetric and lactation pharmacology also apply to OB-GYN clinician–scientists generally. This includes the need to enhance mentorship, expand support for trainees and early career investigators, eliminate systematic disincentives to the incorporation of therapeutic research in clinical practice, and invest in new and existing networks.

Recommendation 3A: Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science.

Status: In progress

There has been substantial progress toward the implementation of Recommendation 3A.

3A.a. Develop and support different types of training programs.

Existing training and career development programs excel at preparing future independent investigators, but they lack the capacity to support a critical mass of the next generation of researchers in these fields. Additional resources are needed to sufficiently expand existing opportunities.

3A.b. Develop and support additional training opportunities.

The NICHD Clinical Pharmacology Training Network (CPTN) is expanding its existing pediatric pharmacology training infrastructure to include maternal and obstetric pharmacology. The network supports training programs funded through F, T, and K mechanisms.[11] Planning for the expansion is still in the early stages, but it has potential to affect the available workforce if implemented.

[11] https://grants.nih.gov/grants/funding/funding_program.htm

The MPRINT Hub also offers funding opportunities, including training and career development awards for clinical and postdoctoral fellows and junior faculty focused on pediatric, pregnancy, and lactation research.

There are ongoing efforts through the NIH Pediatric Research Consortium to engage other Institutes and Centers to discuss training and career development, encourage investigators to apply for K and T grants across Institutes, and leverage the opportunities provided under BPCA and the Pediatric Research Equity Act (PREA).

3A.c. Address challenges.

More flexible alternatives to traditional clinical research paradigms may help reduce barriers for clinicians outside major academic institutions to pursue research careers. There continues to be a need for infrastructure to conduct pharmacokinetic (PK)/pharmacodynamic (PD) studies and to emphasize practice-based studies supported by relevant education in clinical pharmacology research. This would serve to expand the scope of participants and providers eligible to engage in the acquisition of knowledge. However, the existing payment model for obstetric care, which is traditionally bundled into one payment, would need to evolve to facilitate research involvement.

Crucially, OB-GYNs are heavily disincentivized from joining the physician–scientist workforce after they complete a residency or fellowship program. There are a number of factors that contribute to this, including limited maternal–fetal research funding, inadequate protected time for investigators who are not established researchers, challenges securing institutional and independent K awards (K23, K08, and K01 programs) as a junior faculty member, and disincentives to conduct research because of compensation structures in the field. There is also a lack of infrastructure to enable those in the workforce of childbearing age to pursue a physician–scientist career path, especially in the obstetrics and lactation space.

Though additional funding is needed to support programs that will expand the maternal–fetal research workforce, a convening of key opinion leaders and stakeholders is equally necessary to reshape the thinking around, and advance solutions that address, the systemic barriers described above.

3A.d. Develop strategies to increase awareness of career opportunities.

Clinicians often disengage from research activities when they move to private practice. Training and engagement programs, however, may be able to facilitate continuation of research beyond the academic context. Several professional societies are interested in collaborating with NICHD and CPTN to increase awareness of career opportunities through society meetings and other interactions with their members. Additionally, more efforts are needed to engage with and promote career opportunities for researchers engaged in basic science research.

Recommendation 3B: Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science.

Status: In progress

There has been limited progress toward implementation of Recommendation 3B. Although NIH has undertaken various initiatives to improve mentorship in general, there have not been specific efforts directed at obstetric and lactation pharmacology.

3B.a. Increase support for mentors.

Financial support to offset the existing responsibilities of well-established and successful mentors has historically been insufficient in T32 programs and other funding mechanisms. Today, this continues to be the case. Ongoing NICHD efforts to address this include a recent Request for Information (RFI) focused on research training and career development from the NICHD Extramural Training and Career Development Working Group.[12]

Additional resources are needed to promote mentorship in obstetrics and lactation pharmacology. As above, this is also true for the OB-GYN field generally, beyond pharmacology.

3B.b. Help mentees find mentors.

There are robust efforts underway to facilitate locating mentors. CPTN allows fellows to connect with mentors from multiple sites across the United States and encourages networking and collaboration among trainees through its annual meeting and its active alumni network.

However, there has been a decline in the number of mentors—in part because senior researchers are seldom replaced with individuals of comparable experience after they retire. This limits the ability to find mentorship for junior investigators.

3B.c. Provide training on FDA requirements and processes.

Existing training programs have initiatives to incorporate regulatory and advocacy education. FDA also leads workshops on topics relevant to pregnancy and lactation, including webinars for health care providers on the Pregnancy and Lactation Labeling Rule[13] (PLLR) and on opportunities for their pregnant and lactating patients to participate in research.

Recommendation 3C: Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics.

Status: Not implemented

Progress on Recommendation 3C has been limited and requires additional attention.

[12] https://grants.nih.gov/grants/guide/notice-files/NOT-HD-24-011.html

[13] https://www.fda.gov/vaccines-blood-biologics/biologics-rules/pregnancy-and-lactation-labeling-final-rule

3C.a. Make changes to educational requirements.

There have been no changes to educational requirements to include clinical research or pharmacology in existing pregnancy and lactation curricula. Moreover, post-professional pharmacology education that reaches OB-GYN generalists in the community is limited.

Crucially, there is a need for additional lactation education across specialties. Pediatricians and obstetricians are well informed about lactation, but other specialties that support the care of these patients do not receive sufficient lactation education.

3C.b. Create training opportunities.

Professional societies are working to distribute information through their membership, via continuing medical education (CME) modules and other means. However, CME modules have not evolved to include pregnancy- or lactation-related content or requirements. There are also ongoing initiatives from the Coalition to Advance Maternal Therapeutics (CAMT) to convene other medical societies to include obstetric and lactation therapeutics training for other specialties. Dedicated efforts and specific initiatives are needed.

3C.c. Develop EHR[14] modules.

Some health care organizations have modules within EHRs to help providers identify individuals eligible for clinical trials. However, these are largely homegrown efforts that do not extend beyond individual institutions. Additional and systematic efforts would be needed to encourage a broader adoption of these tools for identifying individuals eligible for clinical trials and registries.

[14] Although the original recommendation and implementation plan refer to “medical” records, we have opted to update the text to “health” records to better reflect current technology and terminology.

Implementation Progress: Recommendation 4

Recommendation 4: Remove regulatory barriers to research in pregnant women.

4A. Modify subpart B of the Common Rule[15]:

- **Change 46.204(e)[16] 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 fetus and to align with parental consent for pediatrics.**
- **Add in the option of "minor increase over minimal risk" from subpart D[17] to 36.046.[18]**

Recommendation 4A: Modify subpart B of the Common Rule.

Status: Not implemented

Recommendation 4A has not been implemented.

4A.a. Collect data to inform proposed rulemaking.

There is a need to quantify what fraction of pregnant individuals are being denied the ability to participate in studies that hold the prospect of direct benefit solely to the fetus because of the requirement to obtain parental consent.

4A.b. Encourage OHRP to initiate rulemaking.

Per the 2024 OHRP written update provided to the working group, OHRP has not engaged in additional rulemaking.

The provision at 45 CFR 46.204(e), which applies to research that holds out the prospect of direct benefit solely to the fetus, currently requires that "the consent of the pregnant woman and the father" both be obtained, unless the father is unavailable or the pregnancy resulted from rape or incest. However, 45 CFR 46.204(d) specifies that the pregnant woman's consent is sufficient for research that has the potential to benefit the pregnant woman alone or the pregnant woman

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[15] The bolded text represents the original recommendation in the 2018 PRGLAC Report. However, as noted in the 2020 PRGLAC Implementation Plan, subpart B of 45 CFR 46 is technically not considered part of the Common Rule; that is limited to subpart A of 45 CFR 46. The correct references have been used throughout the text of the present report.

[16] This refers to 45 CFR 46.204(e), in subpart B.

[17] Within subpart D of 45 CFR 46, the language on research involving a minor increase over minimal risk can be found, specifically, under 45 CFR 46.406.

[18] The 2018 PRGLAC Report should have read "45 CFR 46.204" (on research involving pregnant women or fetuses, in subpart B).

and the fetus, as well as for research with no prospect of benefit to the pregnant woman or the fetus when the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.

The written update says that OHRP needs to consult with leadership at the Office of the Assistant Secretary for Health and the Office of the Secretary regarding Recommendation 4A and whether the department would be supportive of the rulemaking.

4A.c. Convene experts to define what constitutes "minimal risk" for a pregnant woman and fetus.

Further action is required to convene experts and stakeholders to reach consensus on what constitutes a minor increase over minimal risk. Recommendation 4A also proposed modeling modifications in 45 CFR 46, subpart B, upon language in subpart D—which outlines additional protections for children involved as subjects in research—to enable flexibility where risks to the fetus represent a "minor increase over minimal risk." FDA regulations for the protection of children in clinical investigations[19] generally align with HHS parental permission requirements for research that involves children as subjects.[20]

[19] 21 CFR 50, subpart D.

[20] 45 CFR 46, subpart D.

Implementation Progress: Recommendation 5

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

5A. 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.

5B. Engage stakeholders such as HHS, professional societies, industry, advocacy groups, and public and global partners.

Recommendation 5A: 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.

Status: In Progress

Recommendation 5A has shown progress toward implementation. However, implementation has occurred on an agency-by-agency basis; there has been no systematic or coordinated effort directed at active (versus passive) engagement. At present, these efforts divert existing resources and are not adequately resourced or prioritized to deliver on the recommendation as written.

5A.a. Conduct a needs assessment and environmental scan to identify the federal agencies and other stakeholders that should be involved in conveying the message of inclusion of pregnant women and lactating women in research, and how best to convey that message to each audience.

Neither a formal needs assessment nor an environmental scan has been conducted. Various federal agencies (CDC, NIH, FDA) working to highlight the importance of pregnant women and lactating women in research would benefit both from additional investment and from a formal needs assessment and an environmental scan.

CDC's communications research efforts have been using patient and health care provider surveys to identify barriers and enhance information dissemination around continuing to take medications during pregnancy. Although this remains ongoing, it has led to improved digital resources and communications strategies to engage with pregnant women. CDC's efforts could be used as a model for future work.

5A.b. Using a logic model, develop a communications plan/public awareness campaign to encourage inclusion of pregnant women and lactating women in research on therapeutics prescribed to these groups.

Numerous federal agencies—including FDA, NIH, and CDC—publicly disseminate information on the use of medications during pregnancy and lactation. Similar efforts are being conducted by professional societies and other stakeholders, such as SMFM, ACOG, and MotherToBaby. However, there has been no systematic or coordinated strategy aimed at active engagement. There is a need for a coordinated public awareness campaign to publicize that this information is available and explain how to access it.

These efforts are currently not adequately resourced or prioritized to deliver on the recommendation as written.

5A.c. Pilot tailored risk communication messaging for each stakeholder audience.

CDC is in the process of assessing one aspect of risk communication through its birth defects case control study, the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), which includes an analysis of women's discussions with health care providers about treatment options for specific conditions during pregnancy. Another ongoing project is assessing risk perception during pregnancy and testing communication strategies within multiple scenarios.

There is a need for health education research focused on how to communicate the complementary risks of not taking medications during pregnancy and lactation. This should include clear messaging about the connection between uncertainty regarding the risks of taking a medication and the need for more research to fill those knowledge gaps, as well as how to get involved in that research.

Furthermore, the WG emphasizes that limited progress has been made in communications efforts to discuss the risks to the mother and child of not breastfeeding.

Recommendation 5B: Engage stakeholders such as HHS, professional societies, industry, advocacy groups, and public and global partners.

Status: Not implemented

Recommendation 5B has not been implemented. Lack of clear ownership for this recommendation has been a barrier to implementation.

5B.a. Keep core messaging simple and consistent.

CDC has conducted work to identify effective messaging strategies, and further communications research is ongoing. However, these strategies have not been systematically implemented.

MotherToBaby[21] uses core messaging strategies for pregnancy and lactation exposures that are standardized and targeted to the lay audience, but these messaging strategies have not been evaluated.

5B.b. Determine effective methods to reach each audience.

CDC survey findings have indicated that although OB-GYNs are the main trusted source of information during pregnancy, patients also rely heavily on advice from friends and relatives, as well as blogs and social media. Survey participants reported feeling more confident in their decision to use medication if messages from clinicians were consistent across providers and validated by personal stories and other sources they trusted. CDC works with clinical organizations, such as ACOG and SMFM, to ensure consistent recommendations, advance health care provider education, and engage trusted messengers.

However, these activities are still ongoing; as stated above, there is no systematic or coordinated effort to deploy these strategies with patient-facing partners (see Recommendation 5A).

5B.c. Develop action plans for each audience.

There is still a need for clear calls to action for intended audiences, in terms of both public awareness campaigns and provider education campaigns. Exploring other opportunities to expand these conversations into the lactation expert community will be key to strengthening the connectivity between different stakeholder groups. This also speaks to the interconnectivity among provider training, research efforts, and public awareness (see Recommendation 6A).

There are numerous stakeholder-driven efforts. However, an ecosystem-wide strategy or plan has not been established. MotherToBaby is one stakeholder-driven example and could serve as a model for what could be developed. A dedicated funding stream for this ecosystem-wide strategy is necessary for implementation.

[21] https://mothertobaby.org/

Implementation Progress: Recommendation 6

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

6A. Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs.

6B. Increase the engagement of health care providers to disseminate information from research findings to their patients.

6C. Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries.

6D. Develop appropriate strategies for sharing and interpreting research findings and risk.

Recommendation 6A: Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs.

Status: In progress

Implementation of Recommendation 6A is ongoing.

6A.a. Foster two-way communication between the research community and health care providers about obstetric and lactation therapeutic research needs.

NICHD released an RFI to solicit nominations for potential priorities on research needs for specific therapeutics used by pregnant, lactating, and postpartum populations. This is a step toward establishing two-way communication that promotes the consideration of conditions that represent the most significant therapeutic uncertainties in pregnant women and lactating women (see Recommendation 8B and Recommendation 9A).

6A.b. Increase health care providers' awareness of obstetric and lactation therapeutic research needs.

There are ongoing efforts through professional societies and MotherToBaby to increase providers' awareness of obstetric and lactation therapeutics research. However, as previously mentioned, additional efforts are needed (see Recommendation 5).

6A.c. Encourage health care providers' engagement by increasing continuing education opportunities.

Creating an online hub and education campaign could enhance health care providers' communication with their pregnant and lactating patients about medication use and research participation. Professional organizations that offer subspecialty care to pregnant women and

lactating women beyond OB-GYNs could incorporate these topics into their CME modules and certification requirements, perhaps in collaboration with certifying bodies. Additionally, more progress is needed in pre- and post-professional contexts (e.g., CME modules, training programs).

Recommendation 6B: Increase the engagement of health care providers to disseminate information from research findings to their patients.

Status: In progress

Progress has been made toward Recommendation 6B. However, implementation has not been coordinated or systematic. This recommendation also would benefit from having a clearly defined owner.

6B.a. Maximize existing resources, adapting for use by health care providers and their patients.

MotherToBaby hosts LactRx, a free app that provides access to LactMed, a database hosted by the National Library of Medicine (NLM) that offers up-to-date information on the use of medications, vaccines, diagnostic agents, and drugs of misuse during breastfeeding. While NLM continues to support web access to LactMed, LactRx offers app-based access to the resource. MotherToBaby has collaborated with the Academy of Breastfeeding Medicine to disseminate information about LactRx. However, additional coordinated efforts are needed to reach lactation consultants and inform them of this resource.

CDC has several initiatives to deliver clear messaging and translate new research findings into actionable content for general audiences. Examples include sharing short videos on social media to combat misinformation, posting patient testimonials that include key information in the caption, and providing links to additional resources. CDC partners with MotherToBaby, which provides insight into common concerns among its audience and helps disseminate updated information more broadly. There are no resources or current plans to broaden the publication and sharing of these resources.

6B.b. Partner with professional societies to facilitate health care providers' knowledge of and access to information about research findings relevant to pregnant women and lactating women.

Federal agencies collaborate with MotherToBaby, ACOG, SMFM, and other organizations to provide educational webinars and materials for clinicians. Other collaborations include the Health Resources and Services Administration's National Maternal Mental Health Hotline, which can transfer callers to MotherToBaby for information on medications or other exposures during pregnancy and lactation.

6B.c. Partner with professional societies to facilitate health care providers' knowledge about clinical trials on therapeutics in pregnancy and lactation.

Several governmental agencies, such as FDA, provide lists of pregnancy exposure registries and other resources, but registry accessibility continues to be a challenge. There are ongoing efforts through ACOG, SMFM, and other professional societies to address barriers to data collection and promote registry education among health care providers who directly interact with patient communities.

Importantly, these efforts are independent from one another and not part of a single, cohesive communications strategy (see Recommendation 13). More work is needed to actively engage with communities.

Recommendation 6C: Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries.

Status: Not Implemented

Recommendation 6C has shown limited progress. Lack of a clear owner has been a barrier to implementation.

6C.a. Establish and maintain a readily accessible website to increase awareness of clinical research opportunities.

Resources exist to identify active or completed clinical trials. For example, ClinicalTrials.gov is a comprehensive, public-facing site. FDA also hosts webinars for health care providers on the PLLR and on opportunities for their pregnant patients and lactating patients to participate in research. In addition, FDA maintains a website listing of pregnancy registries.[22]

However, more work is needed to establish a centralized online hub of information on clinical trials and registries that enroll pregnant women and lactating women and ensure that this is a user-friendly tool.

6C.b. Assist health care providers in finding time for discussions with patients about participating in research.

Compensation structures in both academic and private-practice settings continue to reward clinicians for high-volume patient care but do not incentivize or allow time for enrolling patients in registries or clinical trials. Current clinical workflows are therefore not conducive to finding additional time for providers to discuss research participation with their patients. This represents a field-wide problem in obstetrics and lactation that is not unique to pharmacology and therapeutics research (see Recommendation 3).

[22] https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries

6C.c. Explore incentives for health care providers to discuss clinical trials with their patients.

No specific effort has been undertaken to develop and provide incentives for providers to discuss clinical trials with their patients.

6C.d. Include health care providers in planning for clinical trials.

Typically, disease-focused studies (clinical trials and/or registries) are designed by disease area specialists. Although some clinical trials are designed and executed by individuals with expertise in pregnancy and lactation, there have not been efforts to systematically engage providers with this expertise. A more coordinated effort at the funding level is needed.

Recommendation 6D: Develop appropriate strategies for sharing and interpreting research findings and risk.

Status: In Progress

There has been moderate progress toward implementation of Recommendation 6D.

6D.a. Identify and reduce costs that may pose barriers to accessing information.

New research findings are largely disseminated through professional journals and other publications that require paid subscriptions. MotherToBaby, some professional societies, patient- or consumer-facing organizations, and other organizations offer summaries and newsletter articles to their audiences. However, there have not been systematic efforts to reduce costs to access information that exists behind paywalls and make research results more widely available to medical consumers and practicing clinicians who care for pregnant women or lactating women.

6D.b. Share research results with participants and their health care providers.

Existing communication avenues are largely designed to disseminate findings among relevant research communities. Programs such as MotherToBaby share research findings with participants. More focused attention is needed to communicate findings back to research participants and health care providers, who have historically been overlooked in research dissemination.

6D.c. Explore mechanisms by which to appropriately share data.

Some of this ongoing work is taking place via mechanisms that predate the 2020 PRGLAC Implementation Plan. Existing safety surveillance systems—such as FDA's Sentinel Initiative—could be further leveraged to assess product safety and disseminate study results to inform clinical guidelines.

Implementation Progress: Recommendation 7

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.**

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.

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

Status: In progress

Progress has been made toward implementation of Recommendation 7A.

7A.a. Convene a panel with specific legal, regulatory, and policy expertise to develop a framework for addressing liability issues when planning or conducting research with pregnant women and lactating women.

The Fiscal Year 2022 Consolidated Appropriations Act (P.L. 117-103) called on the National Academies of Sciences, Engineering, and Medicine (NASEM) to examine the real and perceived risks of liability in research conducted with pregnant women and lactating women. The study was sponsored by NICHD and carried out by NASEM.

In April 2024, NASEM's Committee on Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons released the study report.[23] According to study findings, there is limited evidence of legal liability for inclusion of pregnant women and lactating women in clinical research.

The publication of the NASEM report fulfills this implementation step.

[23] National Academies of Sciences, Engineering, and Medicine. 2024. *Advancing clinical research with pregnant and lactating populations: Overcoming real and perceived liability risks.* Washington, DC: The National Academies Press. https://doi.org/10.17226/27595

7A.b. Systematically pursue a research agenda to inform and enable the use of therapeutics by pregnant women and lactating women.

Conducting appropriate preclinical studies, as called for in this recommendation, is a required component of therapeutics development and marketing in the United States.

The report makes several recommendations in line with existing PRGLAC recommendations, and progress toward this step could be made as relevant agencies implement the NASEM recommendations.

7A.c. Identify elements of the VICP applicable to a program of research on therapeutics used by pregnant women and lactating women.

The NASEM report outlines the benefits and limitations of a mechanism to compensate individuals harmed over the course of research, similar to the VICP.

7A.d. Determine whether legislation would be required to establish a program of research.

The NASEM report outlines legislative options for consideration. Policy makers may consider whether federal agencies' existing authority is sufficient for establishing a program to facilitate research and reduce liability for researchers—on their own or in partnership with private entities—or whether new authority is required.

7A.e. Develop options for funding this program.

This step has not been acted on, because it is contingent upon policy makers' decisions on whether existing programs are sufficient or new programs are required to be implemented to address liability mitigation.

Recommendation 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.

Status: Not implemented

Recommendation 7B has not been implemented. No such incentive program or additional authority has been granted to FDA, because the NASEM report is only recently published. Policy makers may consider whether federal agencies' existing authority is sufficient for establishing a program to facilitate research and reduce liability for researchers—on their own or in partnership with private entities—or new authority is required.

7B.a. Identify the studies needed to obtain clinically relevant data to inform dosing and safety of therapeutics used by pregnant women and lactating women.

NICHD published an RFI seeking nominations for research priorities for therapeutics used by pregnant, lactating, and postpartum persons (see Recommendation 8B and Recommendation 9A). With that, the prioritization process described in this step is fulfilled.

7B.b. Analyze the BPCA program for lessons learned on obtaining data from pharmaceutical manufacturers or whether government-funded studies are required to obtain these data.

The NASEM report includes an assessment of BPCA and provides a detailed analysis of lessons learned as part of the pediatric BPCA program.

7B.c. Obtain sufficient data on the use of therapeutics by pregnant women and lactating women.

The NASEM report recommends an expansion of authority similar to the one established by PREA to require research related to the use of drugs, biologics, vaccines, and medical devices in pregnant women and lactating women.

7B.d. Support additional research to add to the evidence base for new therapeutic products that may be used by women who are or may become pregnant or by lactating women.

This subrecommendation is addressed by Recommendation 2.

Implementation Progress: Recommendation 8

Recommendation 8: Develop separate programs to study therapeutic products used off patent in pregnant women and lactating women using BPCA as a model.

8A. Provide specific funding.

8B. Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women.

Recommendation 8A: Provide specific funding.

Status: Not implemented

Recommendation 8A has not been implemented and may require additional resources and congressional action to be realized.

8A.a. Establish infrastructure to carry out testing of drugs commonly used in or with high impact for pregnant women and lactating women.

Additional resources and congressional action may be required for this implementation step to be actionable.

8A.b. Maximize use of existing data.

Existing data sources have not yet been explored to determine whether they are suitable to evaluate the safety of off-patent products, particularly in pregnancy. Specific funding may be required. More funding may be necessary to create incentive structures (including monetary compensation for time spent) for health care providers and generic manufacturers to contribute data to registries.

8A.c. Develop technology.

This step is in progress through programs such as Complement-ARIE (see Recommendation 2A.c). Additional resources may be necessary to promote the development of technology that could potentially substitute for or augment human clinical trials to expedite research on therapeutics used by pregnant women or lactating women.

Recommendation 8B: Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women.

Status: Implemented

Recommendation 8B has been implemented.[24]

8B.a. Consider the NIH BPCA prioritization process as one model for developing a prioritization process for testing therapeutics used by pregnant women and lactating women.

In 2023, NICHD issued an RFI inviting nominations for potential priorities on research needs for specific therapeutics used by pregnant women, lactating women, and postpartum women.[25] When the public comment period closed, in September 2023, 136 nominations had been received. The majority of the nominations were for drug research (114) versus vaccines (2) or dietary supplements (20) and related to general medical conditions (79) versus conditions that are lactation-specific (22) or pregnancy- or postpartum-specific (35). After concluding its internal administrative review of the nominations, NICHD will convene stakeholders to discuss the initial nomination list and continue gathering input on a preliminary list of prioritized drug, vaccine, and dietary supplement research needs. NICHD expects to finalize and publish the initial priority list in mid-to-late 2025. Once published, the priority list would serve to influence NIH funding opportunities in the field.

8B.b. Establish separate prioritization processes and programs for testing therapies and/or conditions in pregnant women and lactating women.

Although issuing this RFI was an important accomplishment, additional activity and resources are required to continue efforts beyond the inaugural cycle and establish a sustained process going forward.

[24] There was no clear consensus among the WG members on the status of this recommendation. Some believed that NICHD's RFI fulfilled this recommendation; others believed that, although significant, this did not constitute sufficient progress to consider Recommendation 8B fully implemented.

[25] https://grants.nih.gov/grants/guide/notice-files/NOT-HD-23-013.html

Implementation Progress: Recommendation 9

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

9A. Create separate prioritization processes for pregnant women and lactating women.

- **Unmet needs in lactation include low milk supply and mastitis.**
- **Unmet needs in pregnancy include preterm labor and hyperemesis.**

9B. Create a Biomedical Advanced Research and Development Authority (BARDA)–like model and the NIH vaccine model that takes clinical development up to Phase II.

Recommendation 9A: Create separate prioritization processes for pregnant women and lactating women.

Status: Implemented

Recommendation 9A has been implemented through the creation of NICHD's RFI.[26]

9A.a. Identify a process for prioritizing the development and manufacture of new drugs and therapeutics for conditions arising during pregnancy and lactation.

Similar to Recommendation 8B, NICHD's RFI to prioritize research needs in specific therapeutics for pregnant women, lactating women, and postpartum women was an important step toward implementation of Recommendation 9A. Of the top 10 therapeutic areas indicated in the nominations, preterm labor ranked third (11 nominations), and milk supply ranked seventh (8 nominations).

Once again, there is a need for additional resources to ensure that similar processes can be implemented in the future.

[26] There was no clear consensus among the WG on the status of this recommendation. As with Recommendation 8B, some WG members believed that NICHD's RFI fulfilled this recommendation, whereas others felt that issuing the RFI was key but did not constitute sufficient progress to consider the Recommendation 9A fully implemented.

Recommendation 9B: Create a BARDA-like model and the NIH vaccine model that takes clinical development up to Phase II.

Status: Not implemented

Recommendation 9B has not been implemented and may be contingent on congressional action.

9B.a. Establish a new federal program to foster drug discovery and the clinical development of therapeutics for conditions specific to pregnant women and lactating women.

Additional financial resources and congressional action may be necessary for a BARDA-like model and similar initiatives to be put into place and made sustainable.

9B.b. Provide incentives to industry for research on therapeutics to treat conditions specific to pregnant women or lactating women.

More funding or additional regulations may be required to create incentive structures to engage the pharmaceutical industry in research specific to pregnant or lactating women.

9B.c. Establish the infrastructure needed for this new program.

Building a program to develop and test therapeutics to treat conditions specific to pregnant women or lactating women would require congressional authorization and dedicated funding.

Implementation Progress: Recommendation 10

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

10A. Investigators/sponsors must specifically justify exclusion in study design.

10B. Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation.

10C. Develop a systematic plan on how data for pregnant women and lactating women will be obtained in a timely fashion to include PK/PD and safety.

10D. Develop guidance for IRBs and investigators about the inclusion of pregnant women and lactating women in research.

10E. Develop a systematic plan for when a woman becomes pregnant in a study to include whether the product should continue,[27] whether unblinding is necessary, and how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information.

Recommendation 10A: Investigators/sponsors must specifically justify exclusion in study design.

Status: Not implemented

Although FDA draft and final guidance documents address the inclusion of pregnant women and lactating women, there is no specific guidance recommending justification for exclusion of these populations from research. Other government agencies and nongovernmental entities may have a relevant role to play in shaping research guidance specific to justification of exclusion of pregnant women and lactating women from trials.

10A.a. Account for investigators and sponsors alike.

Multiple FDA final and draft guidance documents address inclusion of pregnant women and lactating women in research. However, there are no specific FDA guidance documents that recommend investigators justify the exclusion of these populations in study design.

There have been no specific policies that require justification for exclusion of pregnant women or lactating women from NIH-funded research trials. Although investigators must justify the exclusion of nonpregnant women and members of racial and ethnic minorities from NIH-funded trials, there is no requirement for such justification when excluding pregnant women or lactating

[27] As noted in the 2020 PRGLAC Implementation Plan, this refers to whether the product being tested should continue to be used by the pregnant woman who participate in the study.

women.[28] Likewise, investigators' annual progress reports must track enrollment by sex and gender, race, and ethnicity, yet nothing requires them to track inclusion of pregnant women or lactating women. Changes to NIH inclusion policies would be required to advance this implementation step.

Per the 2024 OHRP written update, OHRP has not released additional guidance to facilitate the conduct of research that involves pregnant or lactating women.

Involvement of other government agencies and nongovernmental entities—including academic institutions, industry stakeholders, and ethics committees tasked with the protection of human subjects—in shaping research guidance specific to justification of the exclusion of pregnant women and lactating women from clinical trials could help facilitate research with these populations. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is currently developing a global guideline on the inclusion of pregnant women and lactating women in clinical research.[29] This will be a road map that all ICH regulatory agencies (of which FDA is a member) will be committed to adopting.

10A.b. Account for sponsors (i.e., drug developers).

The 2020 PRGLAC Implementation Plan proposed that FDA require drug developers to provide a "PRGLAC Study Plan" and "PRGLAC Assessment" during the product development process. For products under development that would likely be used in females of reproductive potential, drug developers would be required to outline the available data, the existing gaps in evidence, and the data that will be collected to support appropriate labeling of the product when used during pregnancy, lactation, or both.

FDA does not have the authority under its implementing statutes to require drug developers to provide such a PRGLAC Assessment and Study Plan. To implement this recommendation, congressional action is required.

10A.c. Establish criteria that would describe certain circumstances in which drug developers would not be required to submit a "PRGLAC Study Plan" and "PRGLAC Assessment."

This step proposed that FDA lead a process involving relevant stakeholders to specify the criteria that determines whether a drug developer would need to submit a PRGLAC assessment and study plan for a certain product.

10A.d. Establish criteria that would allow drug developers submitting new drug/biologics license applications to receive a waiver or deferral for the PRGLAC assessment and study plan.

Under this recommendation, FDA would be authorized to grant a drug developer a full or partial waiver or a deferral for submitting a PRGLAC assessment and study plan in select cases. Again,

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[28] https://orwh.od.nih.gov/toolkit/nih-policies-inclusion/guidelines

[29] https://database.ich.org/sites/default/files/ICH_E21_Final_Concept_Paper_2023_1106_MCApproved.pdf

the working group recommends that FDA lead a process to gather input from stakeholders on the appropriate criteria for such provisions. Implementation of this step would be contingent upon Congress granting the FDA authority to require a PRGLAC study plan or assessment.

10A.e. Exclusion of pregnant women or lactating women from clinical research should be justified in investigational new drug applications (INDs) for new drugs/indications or biological products.

FDA already has the authority to review all protocols submitted in an IND, including requesting information about the exclusion of pregnant women or lactating women.

Recommendation 10B: Ensure that studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation.

Status: In progress

Recommendation 10B is in progress, with efforts primarily led through the issuance of FDA guidance.

10B.a. Encourage investigators to follow FDA guidance about trial design and inclusion of pregnant women and lactating women in clinical research.

FDA has previously published draft guidance for industry that touches on the need to collect sufficient PK/PD data to determine the appropriate dosage for different stages of pregnancy and lactation:

- The 2018 FDA draft guidance *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*[30] specifically addresses the collection of PK data during pregnancy.
- The 2004 FDA draft guidance *Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling*[31] specifically discusses study designs to capture PK information pre-pregnancy, during all three trimesters, and postpartum.
- The 2019 FDA draft guidance *Clinical Lactation Studies: Considerations for Study Design*[32] specifically considers types of lactation studies and the collection of PK data based on stages of lactation.

Final evaluation of implementation is contingent on FDA issuing final guidance.

[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents

[31] Ibid.

[32] Ibid.

10B.b. Prioritize the development of new models for testing the effects of drugs/biologic products.

There are ongoing efforts to expand the number of nonclinical models available to conduct safety and PK/PD studies in pregnant women and lactating women. However, there needs to be more investment in basic research to develop *in vivo*, *in vitro*, and computational models for safety testing and PK/PD that can be used to de-risk candidate drugs for clinical trials (see Recommendation 2A).

Recommendation 10C: Develop a systematic plan on how data for pregnant women and lactating women will be obtained in a timely fashion to include PK/PD and safety.

Status: In progress

Recommendation 10C has shown some progress, with its individual implementation steps in different stages of execution.

10C.a. Ensure that data from publicly funded studies on drugs and biologics used by pregnant women and lactating women are made widely available to the research community.

Progress has been made to increase the availability of data from publicly funded studies on therapeutics used by pregnant women or lactating women to conduct further research.

Studies carried out within NICHD clinical trial networks feed the collected trial data into DASH. This allows other researchers to access de-identified trial data and request biospecimens from selected studies.

The MPRINT Knowledgebase and Portal Core is developing a knowledge base of data and resources related to maternal and pediatric therapeutics that occur with and around pregnancy and lactation. These integrated resources will help the research community assess the quality and reliability of evidence and identify gaps to support translational research.

10C.b. Support additional publicly funded research aimed at filling research gaps.

Significant progress has been made through efforts such as NICHD trial networks and the MPRINT Hub. Continued funding to sustain and expand such efforts is needed.

Relevant NICHD trial networks include the MFMU Network, the NRN, and the Global Network (see Recommendation 2A). The recent updates seen by these decades-old networks aim to enhance the rigor and reproducibility of clinical trial protocols, promote greater availability of multisite clinical trial infrastructure, facilitate data sharing and access to biospecimens, and enable greater involvement of diverse populations, with a concrete plan for funding future studies.

10C.c. Authorize FDA to require drug developers that are submitting new drug/biologics license applications to provide a "PRGLAC Assessment" and "PRGLAC Study Plan."

As outlined in Recommendation 10A, FDA does not have the authority to require drug developers to provide a PRGLAC assessment and study plan. Implementation of this step is contingent upon Congress granting FDA the authority to require a PRGLAC study plan or assessment.

Recommendation 10D: Develop guidance for IRBs and investigators about the inclusion of pregnant women and lactating women in research.

Status: Not implemented

Recommendation 10D has shown limited progress toward implementation. FDA has made progress to the extent possible. However, several of the implementation steps for the execution of this recommendation are yet to be addressed.

10D.a. Revise federal regulations to include a definition of what constitutes "acceptable risk" for pregnant women's or lactating women's participation in research, including their offspring.

OHRP has not attempted to redefine acceptable risk. Per the implementation plan, OHRP would need to lead an effort with input from professional societies, women's health organizations, and other interested stakeholders to implement this step.

10D.b. Standardize the informed-consent procedures for enrolling pregnant women and lactating women in clinical research.

There has been no unifying effort to standardize the informed-consent procedures for enrolling pregnant women and lactating women in clinical research. OHRP has not released additional guidance to promote the inclusion of pregnant women or lactating women in clinical research, per its written update to the WG.

Global ICH guidelines on inclusion of pregnant women or lactating women in clinical trials are currently under development.[33]

10D.c. Provide IRBs with recommended practices to facilitate inclusion of pregnant women and lactating women in study designs.

The impact of PRGLAC recommendations on IRB deliberations remains anecdotal. SMFM plans to develop a toolkit for clinician–scientists to educate their IRBs about the inclusion of pregnant women and lactating women in research. However, HHS has not released guidance to provide

[33] https://orwh.od.nih.gov/toolkit/nih-policies-inclusion/guidelines

IRBs with recommended practices for the inclusion of pregnant women and lactating women in study designs.

There may be a need for additional OHRP action for full implementation.

Recommendation 10E: Develop a systematic plan for when a woman becomes pregnant in a study to include whether product should continue,[34] whether unblinding is necessary, and how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information.

Status: Not implemented

Limited progress has been made toward implementation of Recommendation 10E, which is relevant only for pregnancy.

10E.a. Encourage investigators to follow FDA guidance about trial design and inclusion of pregnant women and lactating women in clinical research.

FDA's 2018 draft guidance on inclusion of pregnant women in research[35] specifically discusses considerations for women who become pregnant while enrolled in a clinical trial.

No progress has been made with regard to the PRGLAC Implementation Report's recommendation to develop and disseminate a standardized reconsent template for women who become pregnant to review the risks and benefits of continuing in a trial.

10E.b. In any of these scenarios, collect and report the data on pregnancy outcomes.

There has been no policy action from HHS or other funding agencies to encourage grant awardees to capture and report opportunistic data should participants in their clinical studies become pregnant.

In order to implement the recommendation as written, input from stakeholders outside the federal government may be required. Experts from industry and academia could brainstorm an approach to developing a systematic plan for an instance in which a woman becomes pregnant during a clinical trial.

The ability to do this is available through existing registries. However, this would require additional resources, including the engagement of a third-party convener, which, to date, has also been a barrier to implementation.

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[34] As noted in the 2020 PRGLAC Implementation Plan, this refers to whether the pregnant woman participating in the study should continue to use the product being tested.

[35] https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Implementation Progress: Recommendation 11

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

11A. 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.

11B. Broaden the focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women.

11C. Encourage networks/collaborations to engage in public–private partnerships to facilitate research.

Recommendation 11A: 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.

Status: In progress

Implementation of Recommendation 11A is underway. Additional resources would allow for these activities to be expanded to federal agencies beyond NIH and FDA.

11A.a. Expansion of current networks

Existing networks—including the MFMU Network, the NRN, the Global Network, the Pediatric Trials Network (PTN), and the Sentinel System—have recently been modified to continue to increase funding opportunities and support infrastructure for research with pregnant women and lactating women (see also Recommendation 2).

11A.b. Conduct additional research on therapeutics used by pregnant women and lactating women in currently available research networks.

The aforementioned networks are being utilized to conduct studies on therapeutics used by pregnant women and lactating women. For example, the Chronic Hypertension and Pregnancy (CHAP)[36] trial investigated the safety and efficacy of antihypertensive drugs for treatment of mild chronic hypertension in pregnant women. Findings from this trial changed the ACOG and SMFM guidelines for treating hypertension almost immediately after completion, in 2022. The study was funded by the National Heart, Lung, and Blood Institute and leveraged the NICHD MFMU Network for study sites.

[36] https://www.nejm.org/doi/full/10.1056/NEJMoa2201295

11A.c. Create a new network model specifically for the testing of therapeutics used by pregnant women and lactating women.

Although no new entities have been created, networks such as the MFMU Network and the Global Network have been leveraged to support relevant studies. The MPRINT Hub was created to expand the available knowledge, tools, and expertise about therapeutics used by pregnant women and lactating women. Additional support for new entities would be required to fully implement this step.

11A.d. Develop streamlined processes for collaborations among industry, philanthropy, and government to support clinical research.

Although there is interest in such public–private collaboration, a neutral third-party convener would be needed to bring the relevant stakeholders together. This may require additional resources and congressional action.

11A.e. Review and address the ability of pregnancy registries to maximize enrollment and make data available for research.

NICHD-funded researchers are using DASH to upload specimens and data for future research purposes. Existing pregnancy registries, such as MotherToBaby, can inform avenues to maximize enrollment and make resulting data available for additional research.

Additional work is needed to fully implement Recommendation 11A.e.

11A.f. Facilitate comparative effectiveness trials, trials embedded within clinical care ("pragmatic trials"), and case-control studies.

This step has not been implemented. Crucially, some of the trial designs suggested in this implementation step may not be suitable for use in lactation therapeutics studies. Different trial designs are needed for pregnancy therapeutics studies and lactation therapeutic studies (see Overarching Themes).

Recommendation 11B: Broaden the focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women.

Status: In progress

Significant progress has been made toward Recommendation 11B. Although there has been substantial research on novel drugs for obstetric and lactation conditions, less progress has been made regarding lactation.

11B.a. Provide additional resources to existing networks.

Existing networks (e.g., PTN) are using their resources to fund studies on pregnant women and lactating women. However, they have not received additional funding for these activities.

Additional resources would be needed to fully implement this step.

11B.b. Establishing standards for assessing risk in pregnancy and lactation research.

NICHD's efforts to identify biomarkers and develop nonclinical models demonstrate progress on this front. An example of this is the launch of a new component of the MPRINT Hub to provide a biomarker platform for placental and fetal exosomes. Having biomarkers for risk stratification is important for stimulating translation of potential therapeutics into clinical practice.

NIH's Complement-ARIE program is also expected to promote the standardization and validation of novel methodologies in clinical research, including the advancement of nonclinical models for pregnancy and lactation to assess and reduce the risk inherent in clinical trials (see Recommendation 2A). As NIH expands its investment in the Complement-ARIE program, there may be an opportunity to make further progress toward implementation of this step.

The number of applications to study therapeutics used by lactating women is low. The lack of progress may be due to the difficulty in capturing lactation issues and data. In turn, the low number of lactation studies may constitute a barrier to moving toward target validation. More information is needed to understand why progress in this area is lagging.

11B.c. Establishing relationships with industry to partner on testing of therapeutics used by pregnant women and lactating women.

Implementation of this step has been limited. There is interest in establishing increased partnerships with the private sector, such as through FNIH. However, this action would require a neutral third-party convener.

There is great opportunity for public–private partnerships, especially for lactation. For example, the Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology, and Breastfeeding to Improve Outcomes Now (ConcePTION) is a European project focused on pregnancy and lactation research and funded by the Innovative Medicines Initiative (IMI), a public–private partnership. Among other efforts, the project is working to identify nonclinical models to explore drug transfer through the intake of breastmilk. This work quickly attracted private partners, perhaps in part because of the potential to address knowledge gaps around lactation for labeling purposes when developing drugs that could be passed to the offspring when breastfeeding.

One of the challenges in engaging private companies in pregnancy and lactation research is finding champions within the private sector. Building a coalition of individuals who represent companies and are willing to engage in creating these public–private partnerships may be key for implementation. Perceived liability concerns may also be a barrier for private-sector engagement (see Recommendation 7).

There is a need for more proactive efforts to help educate public, academic, and industry entities about establishing these public–private research collaborations. Additional resources or congressional action may be required to make progress on this recommendation.

Recommendation 11C: Encourage networks/collaborations to engage in public–private partnerships to facilitate research.

Status: Not implemented

There has been limited progress toward implementation of Recommendation 11C. However, there is clear interest in public–private collaborations to facilitate research.

One path to do this may be through FNIH. As an independent nonprofit organization chartered by Congress to support NIH's mission, the foundation establishes partnerships that NIH, as a federal agency, is not permitted to create. One of these partnerships is the Biomarkers Consortium (BC), which funds projects that bridge the gap between basic research and practical needs for advancing drug development and regulatory science.

In February 2024, FNIH launched the first public–private partnership to develop tools to identify pregnant women at high risk of early-onset preeclampsia.[37] This 3-year BC project is a collaboration with NIH and eight other partners that represent life sciences companies, academia, and nonprofit and patient advocacy organizations.

Additional resources and congressional action may be necessary to complete implementation of this recommendation.

[37] https://fnih.org/press-release/the-foundation-for-the-national-institutes-of-health-launches-first-public-private-partnership-for-early-detection-of-preeclampsia/

Implementation Progress: Recommendation 12

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

12A. Design health record systems to link mother and infant records.

12B. Leverage large studies and databases, including health systems, health plans, surveillance systems, EHRs, and registries.

12C. Use novel data resources.

12D. Use innovative methods of data analytics.

12E. Require common data elements (CDEs) to facilitate collaboration and use.

Recommendation 12A: Design health record systems to link mother and infant records.

Status: In progress

Progress has been made toward Recommendation 12A regarding pregnancy. However, this recommendation has not been implemented in the lactation space.

12A.a. Establish an ongoing working group within HHS with data and health records expertise.

NICHD collaborated with federal and private partners to produce a Longitudinal Maternal & Child Health Information for Research implementation guide.[38]

12A.b. Review pertinent existing resources and registries.

Many tools have been developed to create mother–infant linkages, including NICHD's MaternalHealthLink (MHL) project and FDA's use of the Sentinel Common Data Model (SCDM), which leverages insurance claims data from a distributed network of data partners. However, these tools cannot be aggregated. Interoperability, or the ability to share information across systems, may require additional focus.

12A.c. Develop variables and standard protocols for optimal linkages of mother–infant records.

In addition to NICHD's MHL project, efforts are ongoing through the MPRINT Hub to develop linkage algorithms for maternal–infant records, which would enable researchers to evaluate

[38] https://www.nichd.nih.gov/newsroom/news/062623-maternal-guide

maternal exposures and childhood outcomes even when treatment of the mother and child occurred across different health care systems.

There are concerns over information completeness. Challenges include lack of patient-reported outcomes in registries, inability to extend linkages across institutions and EHR systems, discerning linkages for one mother and multiple births, and identifying populations that may be underrepresented because of the nature of the datasets, such as the omission of home births.

Information security, data privacy, and data misuse remain concerns, as linking two public-use datasets increases the risk that data privacy could be compromised. Discussions by technical panel experts are ongoing, but no comprehensive solutions have been identified so far. To implement this step effectively, data protections will need to be in place.

More work is required to implement this step.

Recommendation 12B: Leverage large studies and databases, including health systems, health plans, surveillance systems, EHRs, and registries.

Status: In progress

Implementation of Recommendation 12B for pregnancy is ongoing. However, there may be accessibility and transparency issues that need to be addressed. In terms of lactation, this recommendation has not been implemented.

12B.a. Explore hybrid and nongovernmental efforts that track pregnancy outcomes data.

Large databases and large studies, as referenced in this recommendation, are associated with de-identified (anonymized) patient-level data and/or summarized data. Data are currently stored across many locations, which makes data location a challenge for trained investigators. Discussions are ongoing regarding how to safely and confidentially facilitate data location—particularly reproductive health data—across repositories beyond NICHD's DASH. The MPRINT Hub is also collecting information through the Collaborative Online Perinatal & Pediatric Repository[39] with the goal of characterizing maternal and pediatric biobanks to determine the availability of biospecimens for research on preeclampsia and other adverse pregnancy outcomes.

Data sources would need to be evaluated for accuracy and to factor in their unique areas of bias—such as whether a source includes underrepresented populations. These biases are to be expected when using RWD, and some of these challenges can be mitigated by using computational and other methodologies. Additional concerns include data ownership, the fact that large databases are proprietary and can be expensive or difficult to access, the need for more information about duplication across datasets, and the need for transparency, both for the data and the methods used to accumulate the data.

[39] https://mprint.org/partnership/COPPER

Crucially, funding opportunities under a “maternal and pediatric” category historically showed more activity in the pediatric space. However, interest in the maternal space has grown over the past 2 years, and there are now more applications related to pregnancy and maternal–child or maternal–fetal outcomes. More investigator outreach is needed to promote applications in this space.

A more detailed elucidation of specific barriers and limitations is needed before implementation of this recommendation is possible.

Recommendation 12C: Use novel data resources.

Status: In progress

Progress has been made toward implementation of Recommendation 12C.

12C.a. Support large post-marketing observational studies to evaluate the safety and effectiveness of medication classes during pregnancy and lactation.

FDA’s Active Risk Identification and Analysis (ARIA) system, which is part of the Sentinel Initiative, can be used to monitor medical product safety after approval and to investigate potential risks during pregnancy. However, ARIA does not assess effectiveness of the product.

Support for additional post-marketing observational studies, to assess safety and effectiveness of medication during pregnancy and lactation, has not been evaluated.

BD-STEPS is a population-based case-control study of birth defects and stillbirths. It is an important retrospective arm for assessing safety in a comprehensive post-marketing surveillance approach.

More attention is needed to address the evaluation of effectiveness. Additional tools may be needed to allow for effectiveness analyses.

12C.b. Support studies across multiple drugs using the same infrastructure to conserve resources.

FDA’s use of the Sentinel System SCDM is currently limited in the context of pregnancy and has not been used in the context of lactation.

Recommendation 12D: Use innovative methods of data analytics.

Status: In progress

Progress toward implementation of Recommendation 12D is ongoing but still limited.

12D.a. Identify relevant, innovative methods of data analytics.

NICHD is working to leverage and link large de-identified datasets, including real-world evidence (RWE) initiatives. NICHD's Translational Research in Maternal and Pediatric Pharmacology and Therapeutics NOFO lays the foundation for realizing this recommendation, though full implementation may take years.[40, 41]

12D.b. Use methods of data analytics to link multiple data sources.

There are multiple NIH-wide collaborations to promote the use of large datasets. The Human Genetics Amplifier[42] (HuGeAMP) is a software platform that aggregates, integrates, and analyzes human genetic and genomic data. The Reproductive System Knowledge Portal[43] within HuGeAMP uses genetic associations, functional genomics, and computational results to accelerate research on reproductive traits and conditions.

12D.c. Consider establishing a public–private partnership to develop strategies for using innovative methods of data analytics for research with pregnant women and lactating women.

Progress on this front has been limited. Additional public–private partnerships may be needed to promote innovative methods. There is mutual interest in establishing increased partnerships with the private sector, such as through FNIH. However, this action would require a third-party convener.

Recommendation 12E: Require CDEs to facilitate collaboration and use.

Status: In progress

Progress toward Recommendation 12E is ongoing.

12E.a. Under the auspices of the HHS working group, convene an expert panel to harmonize definitions for the CDEs used in obstetrics, pharmacy, lactation, and pediatrics data ("pregnancy and lactation clinical features").

The Office of the National Coordinator for Health Information Technology (ONC) collaborated with NICHD to begin establishing the data elements and definitions for a maternal health domain, identifying stakeholders, and assembling pilot partners to ensure robust user feedback. The goals of the Draft Maternal Health Data Set were to establish a core set of CDEs necessary for

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[40] https://grants.nih.gov/grants/guide/pa-files/PAR-23-130.html

[41] https://grants.nih.gov/grants/guide/pa-files/PAR-23-131.html

[42] https://kp4cd.org/

[43] https://reproductive.hugeamp.org/

high-quality care, equitable outcomes, and maternal health research, and to facilitate standard implementation and support of core data for maternal health care within implementation guides and health care technology systems. The process included gathering input from industry and federal partners, program officers, health care providers, health information system developers, public health officers, and researchers.

Additionally, the development of women's health-specific CDEs is a goal of the White House Women's Health Initiative (WHRI).[44] As part of this initiative, NIH plans to convene experts across the federal government to identify and develop new CDEs related to women's health that will help researchers share and combine datasets, promote interoperability, and improve the accuracy of datasets when it comes to women's health.

12E.b. Using these efforts as a basis, the expert panel convened by the HHS working group should develop or agree upon CDEs for each stage of pregnancy and lactation, including CDEs specific to race and ethnicity.

The Maternal Health Data Set,[45] which is set to begin the comment process shortly, has 163 de-identified data elements that are shared with other domains and 13 unique maternal health data elements, such as hypertensive disorders of pregnancy and anxiety and depression screens. In the interest of equity, such topics as ethnicity, tribal affiliation, and race, which are routinely used in obstetrics, pharmacy, and pediatrics, are among the CDEs.

Crucially, lactation-specific elements are not included. This may need to be addressed during the comment period.

12E.c. As these CDEs are developed, the HHS working group should determine how to incentivize the use of pregnancy- and lactation-related CDEs across EHRs, surveillance efforts, and research across HHS and other data collection systems.

Several efforts were made to promote data harmonization at NIH regarding pregnant women and lactating women during the COVID-19 pandemic.[46] However, CDEs across EHRs are not well advanced, and CDEs and data dictionaries are not available for many studies. Additional efforts to promote CDEs across systems will be needed before adherence to this data standardization can be required. More information is also needed regarding patient-reported outcomes.

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[44] https://www.whitehouse.gov/briefing-room/statements-releases/2024/03/18/fact-sheet-president-biden-issues-executive-order-and-announces-new-actions-to-advance-womens-health-research-and-innovation/

[45] https://ecqi.healthit.gov/uscdi-quality

[46] https://tools.niehs.nih.gov/dr2/files/pregnancy_report_post_phr_addendum_2023_10_17_508.pdf; https://www.niehs.nih.gov/research/programs/disaster/cde/index.cfm; https://tools.niehs.nih.gov/dr2/index.cfm/resource/24206

Implementation Progress: Recommendation 13

Recommendation 13: Optimize registries for pregnancy and lactation.

13A. Create a user-friendly website for registry listing.

13B. Develop registry standards and CDEs 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.**

13C. Facilitate access to data and transparency of information in registries.

- **Use the Antiretroviral Pregnancy Registry (APR)[47] registry as a model.**

13D. Develop disease/condition-focused registries.

- **Move toward a single registry for all therapeutic products with input from stakeholders.**

Recommendation 13A: Create a user-friendly website for registry listing.

Status: Not implemented

Recommendation 13A has not been implemented. Although some efforts are ongoing in the pregnancy space, more attention is required to include lactation in registries.

13A.a. Identify the elements needed for a registry listing.

No cohesive efforts to identify elements needed for a pregnancy or lactation registry listing have been harmonized. With this said, there are numerous existing registries supported by different agencies.

FDA maintains a pregnancy registry webpage for FDA-approved medical products.[48] However, this list of registries is limited to FDA-approved products. Several working group members noted the importance of ensuring that registries are patient centered. FDA's pregnancy website is also expected to launch an additional listing of all lactation studies that FDA issues as post-marketing requirements. This will help to inform the public and health care providers about lactation studies that are active and enrolling patients.

The National Library of Medicine hosts the web-based platform and database LactMed, with app-based access provided by MotherToBaby through LactRx. SMFM also has plans to establish an

[47] The 2018 PRGLAC Recommendations say "ART" but should have said "APR."

[48] https://www.fda.gov/consumers/pregnancy-exposure-registries/list-pregnancy-exposure-registries

online hub of information on clinical trials and registries that enroll pregnant women and lactating women.

13A.b. Develop a public–private partnership to host a pregnancy/lactation registry listing website.

Additional resources would be necessary for this implementation step to occur. A third-party convener may be required to establish this partnership.

Recommendation 13B: Develop registry standards and CDEs that facilitate input of pertinent data with easy, transparent access to obtain information in real time.

Status: In progress

Recommendation 13B is making significant progress toward implementation for pregnancy. However, less progress has been made in the lactation space.

13B.a. Convene a forum to develop registry standards and CDEs.

ONC is conducting work to establish the data for a maternal health domain, identify stakeholders, and assemble pilot partners to ensure robust user feedback (see Recommendation 12). The comment period for the Maternal Health Data Set will serve to gather input from public and private stakeholders regarding the drafted CDEs.

13B.b. Compile materials for use by forum participants that reflect current knowledge and experience in establishing measures and CDEs for registries.

See Recommendation 13B.a. Additional work is required in lactation.

13B.c. Create standardized templates for information.

ONC has developed relevant CDEs for maternal health research (see Recommendation 12). Additionally, data harmonization and CDEs have been developed within specific disease areas or conditions (e.g., hypertensive disorders of pregnancy). This includes a patient registry that incorporates patient-reported outcomes, clinically reported outcomes, and other biospecimens.

No lactation-specific elements are included.

13B.d. Meet with professional societies to encourage use of these standardized templates.

Implementation of this step has not begun.

13B.e. Explore additional long-term data collection on therapeutics used by pregnant women and lactating women.

This step would need to be undertaken by a public–private partnership of relevant stakeholders to understand the need for data collection, where priorities lie, and how to ensure that the collection and analysis of the data are sustainable into the future. When considering large data manipulation or modeling, significant limitations and privacy concerns with certain AI tools exist that should be examined. A computer scientist may be a helpful addition to the discussion.

Recommendation 13C: Facilitate access to data and transparency of information in registries.

Status: Not implemented

Recommendation 13C has not been implemented.

13C.a. Identify and emulate agencies/stakeholders that already have strong data-sharing policies.

APR[49] includes 61 brand-name drugs and involves 24 manufacturers that collaborate to publish their summarized, de-identified results on the public website every 6 months. Its large sample size, based on 20 years of data collection, provides confidence in the results reported by APR. However, most other registries are not at this stage or do not have the scale to provide such comprehensive data. There are a number of patient-driven registries that may play a role in data harmonization as well.

Critically, data results on the APR website belong to the manufacturers of the various drugs. Further consideration could therefore be necessary to determine where the authority to operationalize this recommendation lies.

13C.b. Develop a data-sharing plan.

This step has not been implemented.

13C.c. Consider partnering with data quality improvement programs.

This step has not been implemented.

Recommendation 13D: Develop disease/condition-focused registries.

Status: Not implemented

Recommendation 13D has not been implemented. Although disease registries exist, no move has been made toward a single registry.

[49] https://www.apregistry.com

13D.a. Build a collaboration between the public–private partnership and other industry representatives to work toward a single registry for therapeutic products used by pregnant women and lactating women.

A third-party convener may be needed to facilitate building a collaboration between the public–private partnership cited in Recommendation 13A. There should also be a clear owner of the registry.

13D.b. Expand the use of disease/condition post-marketing studies.

Disease-based registries are effective for timely data collection, compared with single-product, single-sponsor registries. FDA consistently promotes collaborations among manufacturers to develop a disease-based registry for pregnancy. FDA's focus on encouraging use of disease-based registries is a function of the regulatory review process, where a specific New Drug Application or Biologics License Application or supplement is under review by FDA—not an entire class of agents across multiple sponsors.

Additional consideration is needed to understand the best way to operationalize this step.

Implementation Progress: Recommendation 14

Recommendation 14: The HHS secretary should consider exercising the authority provided in law to extend the PRGLAC Task Force when its charter expires in March 2019.

Status: Implemented

Recommendation 14 was fulfilled in March 2019 with the extension of PRGLAC's charter for 2 additional years.

For this extension, the charter directed the Task Force to provide further guidance on the implementation of the recommendations made in its 2018 report. Those efforts culminated in the PRGLAC Implementation Plan, which was submitted to the HHS secretary in August 2020. With this, the Task Force completed its work in 2021.

Implementation Progress: Recommendation 15

Recommendation 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.

Status: Implemented

Recommendation 15 was fulfilled in 2023 with the creation of the WG.

This recommendation called for an additional advisory body to monitor implementation of the recommendations beyond PRGLAC's own charter. This was reiterated in the 2020 PRGLAC Implementation Plan. In 2023, NICHD formed the WG to fulfill this role.

The WG brings together a similar range of expertise as was present in the Task Force. Based on the overall degree of implementation of the PRGLAC recommendations, the WG advises that its work continue in order to further monitor progress and facilitate implementation.

Overarching Themes

In keeping with the recommendations outlined in the 2018 PRGLAC Report—as well as the implementation steps provided for each of the recommendations through the 2020 PRGLAC Implementation Plan—the progress reported in this document comprises an interrelated response to advance the inclusion of pregnant women and lactating women in clinical research. In framing these implementation updates, several common themes emerged, providing a useful overview of the major steps still needed to continue to move forward.

Distinguishing Between Lactation and Pregnancy

Pregnancy and lactation each have their unique challenges, safety concerns, and resource needs. Consequently, they require distinct research efforts and engagement with specific key stakeholders. Moreover, they need separate funding and monitoring to ensure that they are both adequately addressed. Both populations have been underrepresented in clinical research studies, so tracking data on both groups' participation and exclusion could facilitate progress toward their equitable inclusion.

Assessing implementation progress for each population separately is particularly important, because in many cases, lactation is found to have exhibited insufficient gains and to require further attention. In addition, different trial designs are needed for pregnancy therapeutics studies and lactation therapeutic studies. Importantly, lactation therapeutics include not only medications taken during lactation but also drugs taken specifically to address lactation, which are often overlooked.

Though separate, pregnancy and lactation should also be addressed cohesively to preserve awareness of synergies between the two populations.

Assigning Clear Ownership Over Recommendations

A barrier to implementation for several recommendations was a lack of a clear owner to take charge of the recommendation and be responsible for progress toward implementation. Identifying the primary stakeholders, securing an agreement for ownership over the relevant recommendations, and determining the markers of progress could also help the WG measure the impact of the PRGLAC recommendations over time. Additionally, for some of the recommendations, nongovernmental entities may be the most appropriate owner.

If specific entities or organizations are granted primary responsibility over specific PRGLAC recommendations, the WG also encourages establishing measurable short- and long-term goals, as well as a regular check-in procedure to review both ongoing progress to full implementation and long-term results after implementation.

Engaging Multiple, Diverse Stakeholders

Each of the stakeholder groups represented on the Task Force and the WG—government, industry, clinicians, academics, and women involved in research or taking medication while

pregnant and/or breastfeeding—have a vested interest and critical role in implementing the PRGLAC recommendations.

The health of pregnant women and lactating women is relevant to a wide variety of organizations, including not only federal and academic medical institutions but also industry partners, behavioral scientists, professional societies, and community organizations. Another barrier to implementation for several of the recommendations has been the lack of a neutral third-party convener. There is interest from FNIH and other parties in establishing increased partnerships with the private sector. Engaging multiple stakeholders could enable broader consideration of health during pregnancy and lactation in basic, translational, and clinical research.

More proactive efforts are needed to help educate public, academic, and industry entities about establishing these public–private research collaborations. In the future, inviting a greater variety of organizations to participate may facilitate implementation of the PRGLAC recommendations. Diverse stakeholder participation would also create new opportunities for information sharing and partnership formation to address the recommendations.

Requiring Additional Resources and Congressional Action

The implementation of the PRGLAC recommendations requires additional resources and, in some cases, congressional action. Although scientific and funding discussions must remain separate, funding from a greater variety of sources could influence the formation of new collaborative efforts and enable progress toward filling gaps in basic science and clinical research.

Continuing Assessment of Implementation Progress

Several of the implementation steps require additional efforts to be fulfilled. The WG encourages ongoing assessment and attention to the PRGLAC recommendations to ensure that progress continues.

Conclusion

For decades, the exclusion of pregnant women and lactating women from clinical trials has been culturally ingrained. This has limited the collection of scientific evidence to support the safety and appropriate dosing of medications and other therapeutics used during pregnancy and lactation.

The implementation of the PRGLAC recommendations is driving forward inclusion of pregnant women and lactating women in clinical research. This, in turn, will enable patients and clinicians to make informed decisions about therapeutic management during pregnancy and lactation.

Notably, since the original PRGLAC Report was published, in 2018, maternal mortality and access to adequate health care have gained greater recognition as important public health concerns. Equity, though mentioned under the initial ethical considerations in the 2018 report, was not explicitly built into the recommendations. Equity has been increasingly emphasized across the efforts described in this report, though there is more to be done to address racial inequities and maternal mortality.

With more time and additional resources, more progress can be made to realize the actionable steps outlined in the 2020 PRGLAC Implementation Plan. Continued monitoring will help sustain momentum toward ensuring that pregnant women and lactating women are comprehensively and appropriately included in clinical research.[50]

[50] The content of this report represents the opinions of the WG members and does not reflect the official views or policies of their institutions or component groups or agencies of the U.S. Government.

Appendices

Appendix I: PRGLAC Implementation Working Group of Council Members

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Appendix II: PRGLAC Meeting Agendas

- November 17, 2023
- January 19, 2024
- March 22, 2024

National Institutes of Health

NICHD PRGLAC IMPLEMENTATION WORKING GROUP OF COUNCIL

MEETING 1 AGENDA

November 17, 2023, 12 p.m.–4 p.m. (Virtual)

12:00 p.m.	**Opening Remarks and Introduction** Diana Bianchi, M.D., Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
12:15 p.m.	**Session I: Overview of Original PRGLAC Taskforce and Goals of Current Working Group (Co-Chairs)**
12:45 p.m.	**5-minute stretch break**
12:50 p.m.	**Session II: Recommendations, Cluster D Part I (Registries/Real-world data)** *Speakers:* Katie Vance, Ph.D., Program Officer, NICHD Juanita Chinn, Ph.D., Program Officer, NICHD *Moderated discussion, Q&A with panelists (15 min)*
1:50 p.m.	**10-minute break**
2:00 p.m.	**Session III: Recommendations in Cluster D Part II** *Speakers:* Stephanie Garcia, Office of the National Coordinator for Health Information Technology (ONC) Patricia Bright, Ph.D., and Leyla Sahin, M.D., Center for Drug Evaluation and Research, U.S. Food and Drug Administration *Moderated discussion, Q&A with panelists (15 min)*
2:50 p.m.	**10-minute break**
3:00 p.m.	**Moderated discussion about all topics (Co-chairs)**
3:50 p.m.	**Feedback, summary of discussion, and closing remarks (Co-chairs)**

National Institutes of Health

NICHD PRGLAC IMPLEMENTATION WORKING GROUP OF COUNCIL

MEETING 2 AGENDA

January 19, 2024, 12 p.m.–4 p.m. ET (Virtual)

12:00 p.m. **Opening Remarks and Meeting Overview**

- PRGLAC Implementation Working Group Co-Chairs and NICHD Staff

12:20 p.m. **Session I: Recommendations in Clusters A and E (Clinical Trials/ Drug Development)**

- Nahida Chakhtoura, Branch Chief, Pregnancy and Perinatology Branch, NICHD
- Aaron Pawlyk, Branch Chief, Obstetric and Pediatric Pharmacology and Therapeutics Branch, NICHD
- Camille Fabiyi, Program Officer, Obstetric and Pediatric Pharmacology and Therapeutics Branch, NICHD

1:05 p.m. **Moderated Discussion on Clusters A and E**

2:00 p.m. **Break**

2:15 p.m. **Session II: Recommendations in Cluster C (Policy and Regulatory)**

- Kevin A. Prohaska, Associate Director/Senior Bioethics Consultant, Office of Clinical Policy, Food and Drug Administration
- Lynne Yao, M.D., Director, Division of Pediatric and Maternal Health, Center for Drug Evaluation and Research, FDA

2:55 p.m. **Moderated Discussion on Cluster C**

3:50 p.m. **Wrap up and Adjourn**

National Institutes of Health

NICHD PRGLAC IMPLEMENTATION WORKING GROUP OF COUNCIL

MEETING 3 AGENDA

March 22, 2024, 8:30 a.m.–4 p.m. ET (Hybrid) NIH Campus Building 31/6C Room A

8:30 a.m. **Welcome and Coffee**

9:00 a.m. **Opening Remarks and Meeting Overview**

- PRGLAC Implementation Working Group Co-Chairs and NICHD Staff

9:15 a.m. **Session I: Recommendations in Cluster B (Education, Outreach, Training, and Career Development)**

- Lesly Samedy Bates, Pharm.D., Ph.D., Program Officer, Obstetric and Pediatric Pharmacology and Therapeutics Branch, NICHD
- Rachel Gandell Tetlow, Senior Director, Government and Political Affairs, American College of Obstetricians and Gynecologists
- Rebecca Abbott, Senior Director of Advocacy, Society for Maternal-Fetal Medicine

10:15 a.m. **Moderated Discussion**

10:45 a.m. **Break**

11:00 a.m. **Session II: Recommendations in Cluster B (Education, Outreach, Training, and Career Development)**

- Christina Chambers, Ph.D., M.P.H., Distinguished Professor, Department of Pediatrics, UC San Diego
- Kara Polen, M.P.H., National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

11:45 a.m. **Moderated Discussion**

12:15 p.m. **Lunch**

1:15 p.m. **Session III: Follow Up on Past Items, Moderated Discussion, and Report Development**

4:15 p.m. **Concluding Remarks**

4:30 p.m. **Adjourn**

Appendix III: PRGLAC Meeting Minutes

- November 17, 2023
- January 19, 2024
- March 22, 2024

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Task Force on Research Specific to Pregnant Women and Lactating Women Implementation Working Group of Council

MEETING 1 MINUTES

November 17, 2023 (Virtual)

Opening Remarks and Introduction

Diana Bianchi, M.D., Director, NICHD

Dr. Bianchi welcomed the participants, noting that one of her missions as NICHD Director has been to protect pregnant women through research instead of from research. Clinicians are currently forced to decide whether to treat preexisting or medical conditions in pregnant and lactating women despite the lack of adequate scientific knowledge regarding the safety and efficacy of these treatments in pregnant people. NICHD was proud to lead the original Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC).

PRGLAC released a set of recommendations in 2018, followed by an implementation plan in 2020. NICHD and other federal agencies have worked to implement the recommendations. For example, NICHD created the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub, a national resource to coordinate and expand the available tools and expertise in this area.

One of the original PRGLAC recommendations was to establish an advisory committee to monitor and report on the implementation of the recommendations. After that committee's charter expired in 2021, a new committee with similar expertise was established to ensure that the steps recommended by PRGLAC are implemented and progress is monitored. By serving on this new PRGLAC Implementation Working Group (PRGLAC WG) of the National Advisory Child Health and Human Development (NACHHD) Council, the participants at this meeting are fulfilling this ongoing charter. Dr. Bianchi emphasized that the PRGLAC WG is uniquely focused on tracking the implementation of the original 15 recommendations, not on developing new ones, and should strive to uncover barriers to implementation and provide suggestions to facilitate the implementation of PRGLAC's recommendations. Dr. Bianchi thanked all the participants for their time and service in this important task.

Session I: Overview of the Original PRGLAC Task Force and Goals of the Working Group

Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation, and Sue Rahman, Pharm.D., Health Data Synthesis Institute, Co-Chairs

Dr. Bucci-Rechtweg provided historical context, saying that Congress established PRGLAC in 2016 with representation from all sectors, including NIH, federal agencies (e.g., the Centers for Disease Control and Prevention [CDC], the Food and Drug Administration [FDA], the Department of Veterans Affairs [VA]), professional societies, industry, academia, and non-profit

organizations, with NICHD as the lead. The 2018 PRGLAC report to Congress included 15 recommendations for promoting the inclusion of pregnant and lactating women in clinical trials. The PRGLAC implementation plan was issued in 2020. The central theme of the recommendations was the need to alter the scientific culture of limited ascertainment of knowledge of therapeutic products' safety and effectiveness for pregnant and lactating women. Additional themes relating to pregnant and lactating women included leveraging expanded existing federal programs and networks, developing a systematic plan to direct data, developing research tools and strategies, considering optimal trial designs, using registries and data sources, establishing a prioritization process for studying therapeutics to be used during pregnancy and lactation, addressing incentives to include pregnant and lactating women in research, and creating partnerships.

The implementation plan called for the creation of an advisory committee to monitor and report on how PRGLAC's 15 recommendations were being implemented, updating regulations, and providing guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical trials. This is the charter of the PRGLAC WG, which will review publicly available materials pertaining to implementation progress, invite speakers from relevant federal and nonfederal entities to discuss implementation progress and barriers, and provide a report to the NACHHD Council, the NICHD Director, and, ultimately, Congress. The PRGLAC WG will hold information-gathering meetings from September 2023 to March 2024, draft its report by April 2024, and finalize the report and share it with the NACHHD Council and Congress by July 2024.

The PRGLAC WG will review the implementation process by using a series of clusters representing five overarching topics:

- Cluster A: conduct of clinical research and trials
- Cluster B: education, outreach, training, and career development
- Cluster C: policy, regulatory issues, and liability
- Cluster D: registries and real-world data (RWD)
- Cluster E: novel drug discovery and development

The PRGLAC WG will consider Cluster D at this meeting; Clusters A and E on January 19, 2024; and Cluster B on March 22, 2024.

Dr. Rahman reviewed the Cluster D agenda, which emphasizes Recommendation 12 ("Utilize and improve existing sources of data to inform the evidence and provide a foundation for research on pregnant women and lactating women") and Recommendation 13 ("Optimize registries for pregnancy and lactation"). Both of these recommendations center on the collection, organization, and utilization of RWD. The likely owners of these activities include the Office of the National Coordinating Centers for Medicare & Medicaid Services, FDA, and NIH. The goal is for the PRGLAC WG to have an understanding of which recommendations have been fulfilled, which are in progress or planned but have a clearly defined owner with sufficient evidence pointing to a timeline for their execution and which have not exhibited any gains and require attention or reconsideration, by March 2024. This diagram will serve as a framework for constructing the report. White is used to indicate that the information needed to make a decision about the recommendation's status is not available. The PRGLAC WG members will have to do additional work offline to identify the correct data sources and review materials to move any white-coded recommendation to a definitive definition.

Dr. Rahman noted that many of the recommendations have subrecommendations. There are about 40 subrecommendations, indicating the complexity of the work ahead. Moreover, it is not possible for the speakers to present in the order of the recommendations in the implementation plan. PRGLAC WG members will need to familiarize themselves with the recommendations to be covered at the meetings ahead of time and record their thoughts as they hear from the speakers.

Dr. Rahman said that for Recommendation 12, the group should consider progress in the area of electronic health record (EHR) systems, common data elements, database and registry infrastructure, innovative methods of data analytics, and RWD analytics. For Recommendation 13, the group should delve into the registry space and focus on progress related to standards, transparency, construction, and access. The overarching operative phrase for all recommendations is "implementation progress." The group is not reframing or revising the recommendations; it is evaluating whether and to what extent they have been addressed. PRGLAC WG members should also identify any other entities that might make helpful presentations and should note major barriers that would derail a recommendation.

Session II: Recommendations, Cluster D, Part I (Registries/Real-World Data)

Presentation 1: Update on NICHD's Support for Leveraging Data Resources

Katie Vance, Ph.D., Program Officer, Obstetric and Pediatric Pharmacology and Therapeutics Branch, NICHD

Dr. Vance discussed what NICHD is doing to leverage large datasets, including real-world evidence (RWE) initiatives. She noted that research for pregnant, lactating, and postpartum patients has lagged behind that for other research populations because of ethical concerns, lack of patient participation in research, sample collection methodologies, shortages in the research workforce, lack of appropriate preclinical models, and the need for novel study designs. To address these challenges, novel methodologies, including linking of existing large datasets, must be used to promote innovation in research for this population.

There is currently momentum in the use of RWD and RWE, driven by the development of artificial intelligence (AI) and machine learning (ML), other technologies, legislation such as the 21st Century Cures Act of 2016, the FDA Advancing Real-World Evidence Program, NIH's 2023 Data Management and Sharing Policy, and recent demonstrations of the utility of RWE for treating patients. Consequently, the NICHD portfolio in data science and/or RWE studies involving pregnant, lactating, and postpartum people has increased significantly over the past decade.

NICHD has taken a multifaceted approach to leveraging data, using Notices of Funding Opportunities (NOFOs), new and existing programs, and NIH-wide collaborations. One key goal of NOFOs for translational research in maternal and pediatric pharmacology and therapeutics is to advance precision medicine among children and adolescents and the pregnant, lactating, and postpartum population through the development of novel generalizable tools, models, and other technologies. Applications proposing ML model systems with multi-omic and clinical data, *in silico* models using RWD, tools using pharmacoepidemiologic data, and AI/ML tools for data extraction, harmonization, and interoperability are encouraged.

NICHD program announcements also support applications leveraging EHR, claims, and FDA and CDC data. Examples of investigator-initiated awards include the Big data apprOaches fOr Safe Therapeutics in Healthy Pregnancies (BOOST-HP) project focusing on novel signals that

pose the greatest risk to healthy pregnancies, a study of AI methods and EHRs for pediatric pharmacovigilance that is looking at pediatric outcomes from mothers' exposure to drugs during and before pregnancy, and a study of maternal COVID-19 vaccination and lactation outcomes that is collecting data to support vaccination during pregnancy and allay fears about vaccinations.

Dr. Vance described a number of existing programs. The MPRINT initiative, made up of four centers or hubs, was established to catalyze research in maternal and pediatric therapeutics. RWE is a crosscutting issue among all the centers. The MPRINT RWE Core is working to use RWD resources to characterize, study, and address research questions on maternal and pediatric physiology, pharmacology, and clinical outcomes, with the ultimate goal of enhancing drug safety and efficacy. Work is also ongoing to develop a linkage algorithm for maternal–infant records to enable researchers to evaluate maternal exposures and childhood outcomes even when treatment of the mother and child occurred across health systems. The ultimate goal is the creation of a curated maternal–pediatric datamart. The MPRINT Knowledgebase and Portal Core is developing a knowledge base of data and resources relating to maternal and pediatric therapeutics that occur with and around pregnancy and lactation. These integrated resources will help the research community assess the quality and reliability of evidence and identify gaps to support translational research.

A new program, the Implementing a Maternal Health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Maternal Health Research Centers of Excellence, consists of 10 research centers working to design and implement research projects to address the biological, behavioral, environmental, sociocultural, and structural factors that affect pregnancy-related complications and deaths. The focus is on populations that experience health disparities.

NIH-wide collaborations to promote the use of large datasets include the Reproductive System Knowledge Portal, which uses genetic associations, functional genomics, and computational results to accelerate research on reproductive traits and conditions; and the Human Genetics Amplifier, a software platform and infrastructure that aggregates, integrates, and analyzes human genetic and genomic data. Other collaborations include the Complement Animal Research in Experimentation program to catalyze the development, standardization, validation, and use of new approach methodologies and the NIH Pediatric Research Consortium to improve child health research collaborations.

The NICHD Data and Specimen Hub (DASH) is a centralized, cloud-based repository for sharing de-identified data and associated biospecimens from clinical studies funded by NICHD. It contains data from more than 210 studies; has approved more than 600 data reuse requests, resulting in nearly 100 publications; and is constantly being improved and modernized.

Dr. Vance summarized the goals for promoting the use of large datasets: expanding data access and ecosystems; identifying novel therapeutic targets and biomarkers; developing tools, algorithms, and software; informing learning health systems; and improving reproductive health outcomes.

Presentation 2: Report on the MaternalHealthLink (MHL) Project

Juanita Chinn, Ph.D., Program Officer, Population Dynamics Branch, NICHD

The MHL project addresses the lack of data needed to analyze how a pregnant woman's longitudinal medical history and socioeconomic and demographic characteristics affect outcomes for both her and her infant by developing a standardized approach to link electronic data on

maternal and infant health to use in studying the effect of medical conditions or interventions on pregnant, postpartum, or lactating women and their infants. The goal was to pilot and produce a final Health Level Seven (HL7®) published standard for distribution to research and public health partners. In creating this new implementation guide (IG) for researchers over a 2-year period, the investigators employed two specific use cases: hypertensive disorders of pregnancy and pregnancy-associated maternal deaths.

Successfully publishing the first Longitudinal Maternal & Infant Health Information for Research IG required identifying tools and strategies to increase widespread adoption of the guide. To this end, automation and standard tools using MHL for research data acquisition was piloted. MHL, an open-source, measure-based application and a unique product that was produced from this project, provides data access and flexibility to accommodate researchers' needs over time.

MHL was customized from NHSNLink, an open-source application for public health reporting developed under contract with CDC's National Healthcare Safety Network (NHSN). NHSNLink's architecture connects securely to EHR systems via a standard open application interface (API). The API extracts data, evaluates data using predefined measures, generates measures and patient-level reports, and submits data directly to NHSN. Contractors customized NHSNLink for MHL, piloted it with a health information exchange (HIE) to automate data collection, and developed measures to support data collection for cohort populations. The measures (i.e., research questions) were the two use case topics. Dr. Chinn reviewed all the pilot tasks and development work that were required to bring the project to a successful conclusion.

In summary, the steps required for this project included obtaining a pilot participation agreement from an HIE or similar health data aggregator, integrating the MHL applications with the pilot site, calculating the two new measures and collecting aggregate de-identified data for the linked mother–child target population, producing a simple Microsoft Power BI visualization of the reported data, and delivering a final report with recommendations for scaling MHL. Future recommendations include conducting a second expanded pilot with a real research study, enhancing MHL security and authentication options, scaling MHL capabilities for identity management, accounting for appropriate resources to support expected data persistence, and developing a maternal health research toolkit.

Moderated Discussion

R. Alta Charo, J.D., the Warren P. Knowles Professor Emerita of Law and Bioethics at the University of Wisconsin at Madison, asked whether the scope of the data sources is international or limited to the United States. Dr. Vance said the R01 and R21 awards she discussed use U.S. data sources. The NICHD portfolio contains pediatric applications that use RWD from international data sources, but the scope needs to be broadened to include pregnant and lactating people.

An attendee asked whether pregnancy exclusions are being tracked in federally funded studies. Dr. Vance said that NICHD has looked at whether pregnancy is used as an exclusion criterion and noted that this is an important topic for the institute.

Rachel Tetlow, noting the progress with EHRs, asked about the safety and security of information shared in the medical records in relation to research, as opposed to the clinical setting, and what steps are needed to ensure the data are not misused. Dr. Chinn said linking two public use datasets increases the risk that data privacy could be compromised. One partial

solution is the use of disclaimers, which, although not sufficient, would at least make people aware of the risks of linking data. These issues are being discussed by technical panel experts and others who acknowledge the problems but have not identified solutions. A barrier to data privacy solutions is the rapidly changing nature of the information.

Janet Hardy, noting Dr. Vance's comments about promoting maternal health equity in IMPROVE, asked whether using EHR and claims data raises equity variables, given that large data sources are poorly recorded and largely missing for many underserved populations, and asked how that is being addressed. Dr. Vance, clarifying that she is not the program officer for IMPROVE, agreed that both the limitations for access to care and biases related to the available data and data generated from RWD represent a problem. However, Johns Hopkins, the awardee for this particular data innovation hub for the Centers of Excellence, has a plan to address and mitigate these concerns using computational and other methodologies, because there will be biases with using RWD.

Eleni Tsigas asked how non-HIE related databases such as private payer and massive data collectors like Premier factor into maternal data linkage and whether anyone is asking for their input. Dr. Chinn said the HHS Office on Women's Health has published an article on maternal health using Premier data that includes data linkages but that she was not sure how it fits with the project she presented. Dr. Chinn added that there are some public-domain publications on Premier data, particularly relating to hypertension linkages, and said she would explore this and provide a more detailed answer. Dr. Rahman asked whether there have been enough conversations with various HIEs to provide insight into logistical or contractual challenges in trying to expand the MHL initiative. Dr. Chinn said that she had noted in her presentation that securing the HIE data and access requires persistence, and she detailed some of the contractual negotiations that were required. Her experience helped show some of the unanticipated challenges that can come up when trying to access data, particularly when contacting multiple HIEs. This area should be expanded upon as the project scales up.

An attendee noted that a number of funding opportunities fall under the heading of either "maternal" or "pediatric" and asked what percentage of funding is going toward maternal versus pediatric studies. Dr. Vance said that a portfolio analysis her branch conducted last year showed more activity in the pediatric space. However, in the past 2 years, interest in the maternal space has grown, and there are more applications relating to pregnancy or looking at maternal–child or maternal–fetal outcomes, probably because of PRGLAC. More investigator outreach is needed to increase the number of applications.

Yasaswi Kislovskiy, M.D., M.Sc., asked what efforts are being made to ensure that the available linked data are representative nationally and whether it is possible for databases to account for transfer of care or regional effects on maternal outcomes. Dr. Chinn said that it is difficult to link nationally representative data when pulling information out of data sources. Typically, vital statistics are used for nationally representative data, but there is a considerable amount of missing information. EHRs, for example, often lack race, ethnicity, gestational age, and demographic information. Representatives from the National Center for Health Statistics working on the MHL project are aware of the missing-data limitation. There have been discussions about linking EHR data to Census data, and there is a very good paper by Barbara Atlas about some of the challenges and successes with different types of data linkage.

An attendee asked how much funding is devoted to underrepresented populations and regions. Dr. Vance said that it could always be better. Often the major players are the ones submitting the

applications and getting funded. NICHD is getting better at recruiting underserved patient populations as well as investigators from these communities and at tracking this progress.

Dr. Bucci-Rechtweg asked Dr. Chinn whether the recommendations for future scaling of MHL on her final slide were actually intentional activities that will be moving forward or more of a wish list. Dr. Chinn said it was probably more of a wish list, but there could be movement as funding becomes available. To that extent, they are probably both recommendations and a wish list, because they are actively being pursued.

Dr. Bucci-Rechtweg asked whether there are other agencies with activities similar to PRGLAC's whose staff should be invited to speak to the group or whether the current schedule of speakers offers a sufficiently representative sample of the types of activities being conducted to address the PRGLAC recommendations. Dr. Chinn suggested that contacting staff at the Office of the National Coordinator for Health Information Technology would be helpful, because they set the standards, as well as staff at the Patient-Centered Outcomes Research Trust Fund, because they funded multiple projects in this space. Dr. Vance suggested contacting CDC.

Session III: Recommendations in Cluster D, Part II

Presentation 1: USCDI+ for Maternal Health

Stephanie Garcia, M.P.H., Branch Chief, Office of the National Coordinator for Health Information Technology (ONC)

ONC is charged with formulating the federal government's health IT strategy to advance national goals for better and safer health care through an interoperable nationwide health IT infrastructure, including by laying the foundation for EHRs and leveraging them to drive value.

The United States Core Data for Interoperability (USCDI) establishes a consistent baseline of harmonized data elements that can be broadly reused across use cases to support patient care and facilitate patient access using health IT as well as other use cases. It can also be used for research purposes. The USCDI, which is expanded incrementally over time, taking into account both anticipated benefits and industry-wide impacts, acts as an interoperable foundation for health information.

Because unique program-specific data systems are sometimes not fully met by the USCDI, the ONC USCDI+ initiative helps government and industry partners build on the USCDI to support specific program needs by applying USCDI processes for submission and harmonization while focusing on programmatic priorities. This allows ONC to better serve federal partners, ensures that extensions build from the same foundation, and creates the opportunity for aligning similar data needs across agency programs.

The maternal health domain was identified as an area of focus during discussions with CDC regarding public health datasets. ONC partnered with NICHD to begin establishing the data, identifying stakeholders, and assembling pilot partners to ensure robust user feedback. The goals of the Draft Maternal Health Data Set were to establish a core set of data necessary for high-quality care, equitable outcomes, and maternal health research and to facilitate standard implementation and support of core data for maternal health care within implementation guides and health care technology systems. The process took care gaps, the likelihood of capturing data through routine documentation, and potential implementation burdens into account. Ms. Garcia provided an extensive list of data inputs and key sources (e.g., industry and federal partner

listening sessions, vital records, Alliance for Innovation on Maternal Health patient safety bundles). Questions to gather feedback were prepared and given to program officers, health care providers, health IT developers, public health officers, and researchers.

The Maternal Health Data Set will launch for comment in a few weeks and open at a later date after completion of the comment process. Ms. Garcia gave an overview of the dataset, which has 163 data elements that are shared with other domains and 13 unique maternal health data elements, such as hypertensive disorders of pregnancy, method of contraception, and anxiety and depressions screens. In the interests of equity, such topics as ethnicity, tribal affiliation, and race, which are routinely used in obstetrics, pharmacy, and pediatrics, are among the common data elements. Currently, lactation-specific elements are not included, and the PRGLAC WG may wish to address that during the comment period.

Ms. Garcia discussed mother–infant linkages, noting that such linkages vary by technology developer, with some EHRs requiring that records be maintained in the same system to continue the linkage and others not linking mother-infant records at all. Records have been linked using a variety of approaches, including the infant's date of birth, the mother's demographic or next of kin, a system trigger to generate a family history for the baby, or portions of an exchange message such as an HL7 Fast Healthcare Interoperability Resources® (FHIR) resource (e.g., Related Person, Encounter, Family Member) or an HL7-Definition V2 Patient Identification Segment.

Ms. Garcia concluded by saying that what ONC is doing with USCDI+ for maternal health falls within the larger wheelhouse of the office's efforts to move toward health IT alignment across HHS through a series of mechanisms aimed at standardizing how the department collects and uses data. This is the foundation of an interoperable infrastructure.

Presentation 2: Experience from FDA Center for Drug Evaluation and Research (CDER) Sentinel System: Using Electronic Health Record Data to Link Mother and Infant Records

Patricia Bright, Ph.D., CDER, FDA

The key elements of the Sentinel's Active Risk Identification and Analysis (ARIA) System include electronic healthcare data (typically insurance claims); a common data model; a distributed network of data partners; pre-defined, parameterized, reusable routine querying tools; and a sophisticated quality assurance process. To populate the distributed database, information on enrollment, demographics, encounter, dispensing, lab tests, and vital signs is gathered across 14 data partners. When a question arises, the Sentinel System can design a study to query the applicable data partners, who maintain physical and operational control of their data behind their firewalls. The partners query their own data and return results to Sentinel, which then provides aggregated, de-identified results. The mother–infant linkage, which was added to the data model in 2018, contains 10.8 million linked live-birth deliveries. Training on using the Sentinel System is available online.

Dr. Bright discussed the use of novel data resources as proposed in Recommendation 12C. She began with Recommendation 12C(a)—"Support large post-marketing observation studies to evaluate the safety and effectiveness of medication classes during pregnancy and lactation"—with the caveat that FDA support of this subpart does not include an evaluation of medication effectiveness or events occurring during lactation. Dr. Bright provided an example of an FDA premarket review of vericiguat, a drug recommended for heart failure (HF) but implicated in

embryo fetal malformations in animal studies. In determining whether a Risk Evaluation and Mitigation Strategy should be required for vericiguat, FDA estimated HF in reproductive-age women and characterized medication use among pregnancies with HF present. The actual use of vericiguat could not be studied because of its premarket status. FDA found that HF was rare among women of reproductive age and that the use of the potentially embryo-toxic HF medication was also rare and determined that labeling would provide sufficient information to ensure that the benefits outweighed the risks. Another relevant study, Risk of Congenital Cardiac Malformations Following Modafinil Use: A Propensity Score Matched Analysis, can also be found on the Sentinel website.

Dr. Bright outlined some of the limitations of the Sentinel System, noting that programming and tools to look at outcomes that are not related to live births are not yet available. Moreover, ARIA is not sufficient to assess some safety issues, including around pregnancy, because of the inability to capture certain health concerns. However, as part of the Prescription Drug User Fee Act VII, a recent commitment letter focusing on pregnancy safety included demonstration projects comparing pregnancy registry studies with insurance claims database studies to assess signal detection and evaluation when drug exposure is common and projects conducting single-arm safety studies compared with insurance claims database studies to understand signal detection when drug exposure is rare. These projects, expected to conclude by September 2027, will help inform an FDA framework for postmarket pregnancy safety. Dr. Bright provided the link to a recent workshop about optimizing the use of pregnancy safety studies.

In addressing Recommendation 12C(b), "Support studies across multiple drugs using the same infrastructure to conserve resources," Dr. Bright noted that FDA uses its Sentinel Common Data Model (SCDM) to look at study class effects but has not done this in the context of pregnancy.

Dr. Bright next discussed FDA's recent work with Medicaid data. Within the Sentinel System, the linkage of mother and infant data is critical for the assessment of medication safety during pregnancy. Medicaid/Children's Health Insurance Program (CHIP) data in the new Transformed Medicaid Statistical Information System (T-MSIS) format were recently converted to the SCDM, and an initial mother–infant linkage was performed. To ensure the most accurate linkage, both the delivery record and infant record must be associated with the same jurisdiction and have the same case number identifier. In addition, the infant's date of birth must be close to the admission and discharge dates on the delivery record. Overall, 61% of mothers' delivery records (4.1 million of 6.7 million eligible) were linked to child records in the Medicaid/CHIP data. Among 49 jurisdictions (46 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands), 34 had linkage rates over 75%; 7 had linkage rates under 15%. A total of 33 jurisdictions have more than 5 years of inclusion of Medicaid data, 16 have less than 5 years, and 4 (Alabama, Kentucky, Nebraska, and Utah) have no inclusion. Dr. Bright cautioned that the completeness and continuity of the data vary from state to state, so care must be taken to ascertain the quality of the data when using it. Dr. Bright noted that there are publicly available resources on the use of the SCDM-formatted database.

Dr. Bright summarized her conclusions with a series of questions based on CDER's experience:

- What has been done in FDA's Sentinel System that might align with Recommendation 12 ("Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant and lactating women")?
    - The Sentinel System currently has 10.8 million mother–infant linked deliveries.
- What barriers were encountered?

    - Lactation was not addressed through the database studies.
    - Best practices for using complementary data sources for post-market safety assessment are still being explored, and programming tools are still being developed.
    - Quality and capture of Medicaid data differ by state.
- What additional resources, policy changes, or regulations are needed to move forward?
    - See the link to the workshop for a current discussion of these issues.

Presentation 3: FDA Updates Relevant to PRGLAC Recommendation 13: Optimize Registries for Pregnancy and Lactation

Leyla Sahin, M.D., CDER, FDA

Dr. Sahin provided an overview of FDA regulatory authorities related to pregnancy registries and discussed FDA's efforts supporting PRGLAC Recommendation 13 ("Optimize registries for pregnancy and lactation").

Although there are 5.5 million pregnancies in the United States each year, pregnant people, who often need treatment for chronic or acute conditions, have historically been left out of drug trials. Most drugs are approved with only nonclinical reproductive toxicology data. Human drug data, which are generally collected after FDA approval, are needed to inform labeling and clinical care. FDA has the authority to require pregnancy safety studies. This is done by issuing pregnancy registries as postmarketing requirements or commitments (PMRs or PMCs). Most recently, CDER has issued two types of pregnancy PMRs: a pregnancy registry and a complementary database study.

FDA efforts supporting Recommendation 13A ("Create a user-friendly website for registry listing") include maintaining a pregnancy registry webpage for FDA-approved medical products. Standard elements and processes are in place for listing a registry. This registry is limited to FDA-approved products, which raises the question of whether there are other needs that could be addressed by a public–private partnership for registry listings outside of FDA's purview.

FDA efforts supporting Recommendation 13B ("Develop registry standards and CDEs that facilitate input of pertinent data with easy, transparent access to obtain information in real time") include publishing a Guidance for Industry on Postapproval Pregnancy Safety Studies for FDA-approved medical products that is currently undergoing revision. Data from pregnant people are being collected in real time through apps. Dr. Sahin asked whether there are other registries outside of FDA's purview that are needed to address CDEs.

FDA supports Recommendation 13C ("Facilitate access to data and transparency of information in registries; use the [Antiretroviral Pregnancy Registry (APR)] as a model"). The very successful APR, which includes 61 brand name drugs, involves 24 manufacturers that collaborate to publish their results on their public website every 6 months. Dr. Sahin noted that data on the website belong to the manufacturers of the various drugs, which raises the question of where the authority lies to operationalize Recommendation 13C. Further discussion on this topic is needed.

FDA supports Recommendation 13D ("Develop disease-/condition-focused registries [by moving] toward a single registry for all therapeutic products with input from stakeholders [and expanding] the use of disease/condition post-marketing studies"). Dr. Sahin noted that disease-based registries have a good track record in terms of timely data collection, compared to single drug, single sponsor registries. FDA consistently urges collaborations among manufacturers to develop

a disease-based pregnancy registry, but this is a complex process and more consideration is needed to understand the best way to operationalize these recommendations.

Moderated Discussion of Session III Topics

Dr. Charo asked why some states were slow or unwilling to implement the inclusion of Medicaid data and whether that is likely to improve. Dr. Bright said being slow is not too concerning because states were given 2 years to transition and there might be other funding priorities. More concerning is having problems arise later in the process, indicating that something is going wrong, such as doing things that throw off the linkage, having eligibility issues, or encountering situations where people get medications before enrollment. This negatively affects the usefulness of the data. Hopefully things will improve, but it is a concern.

Rebecca Abbott asked what happens after the Sentinel studies are completed and how the information gets to clinicians and patients. Dr. Bright said all of the studies are posted on the website. Usually a study is done to answer a regulatory question or address a safety issue. The study results go to the relevant therapeutic division for the decision about whether to take regulatory action, communicate to the public, or make a labeling change. Sometimes the process involves consideration of a new medication, such as Paxlovid (before it was approved).

Dr. Charo asked whether there are examples of arrangements that resulted in companies allowing the use of their proprietary data or any lessons to be learned about how to extract those data for public scrutiny. Dr. Sahin said that it is a complicated process, but the APR figured out a way to do it. She suggested that the PRGLAC WG ask the person who runs the APR to come speak to the group to discuss potential solutions. Dr. Hardy noted that the Antiretroviral Pregnancy Registry is a stellar registry with 20 years' worth of data. Its large sample size provides confidence in the results the APR is reporting. She suggested that most other registries are not at the stage or size to provide such comprehensive data or results and that this should be taken into consideration when making recommendations about registries.

Sharon Nachman, M.D., asked whether allowing pharma to do these registries excuses those companies from testing their products in pregnancy and how off-patent or generic drugs would be handled. Who is responsible for collating the data for generic drugs? Dr. Bucci-Rechtweg suggested that this is not the job of a single stakeholder but rather of a true public–private partnership of relevant stakeholders to understand the need for the data collection, where priorities lie, and how to ensure that the collection and analysis of the data are sustainable into the future. These issues must be addressed for Recommendation 13 to be properly implemented. Dr. Nachman noted that cardiology and neuro-seizure drugs represent a big proportion of drugs given to pregnant populations and wondered whether the next registry should be to determine which drugs—patent or off-patent—should be investigated. She suggested identifying a big disease category and the drugs included in that category and using that as the next step in the database registry. Dr. Bright addressed two of Dr. Nachman's questions, saying that drug companies doing registry-based studies do not get an automatic pass on population-based studies, because FDA guidance can recommend population-based studies. In terms of handling generic drugs, Sentinel can look at generics but has not done so for pregnancy safety. Dr. Bright added that consideration is being given to looking at disease-based databases.

An attendee asked for more insights about how to generate information about lactation. Dr. Pamela Barens noted that mood disorders in the postpartum period and the safety of using medications at that time would be a common clinical concern as related to lactation. Dr. Garcia

said that lactation was not included in the USCDI+ dataset yet, but she would be happy to work with subject matter experts on that project. There are also ways of profiling lactation data in the FHIR resources. Dr. Sahin said that FDA has the authority to issue postpartum requirements for lactation studies. FDA's pregnancy website will soon launch an additional website listing all lactation studies that FDA issues as PMRs to inform the public and health care providers about lactation studies that are active and enrolling patients. Dr. Bright cautioned that large databases using data from insurance claims do not capture lactation data well, so they are not the best resource for lactation studies. Dr. Hardy also questioned the use of large databases for lactation studies, because the large variability in women's lactation practices over a short period of time would be hard to capture. Dr. Sahin added that FDA is looking into tying lactation studies into registries for more exposure.

Dr. Kislovskiy asked about FDA engagement with the Reproductive Toxicology Center (Reprotox), which has emerged as a principal source of information to guide medication use in pregnancy. Dr. Sahin said that FDA has interactions with Reprotox staff and members. She noted again that because the data are owned by the manufacturers, more engagement with them would be warranted, as well as further engagement and discussion with Reprotox.

Katie Schubert, M.P.P., CAE, emphasized the need to make it as easy as possible for clinicians and patients to access information from pregnancy registries, particularly since the information is owned by the drug sponsors.

Julie Grimes suggested that the Women, Infants, and Children Peer Counseling program might be an effective data point for lactation. Another possibility would be using the LactMed database as a way to gather data based on the type of information users are looking for.

Ms. Tsigas asked whether there is value in connecting with other resources to investigate data harmonization for pregnancy research. There are a number of patient-driven registries that might play a role in the data harmonization work.

Moderated Discussion—All Topics

Dr. Rahman asked the group to identify the recommendations or supplements that do not require additional discussion because they have either been fulfilled as outlined in the implementation plan or have enough momentum that they are far enough along to be considered ongoing/planned.

Recommendation 12: Dr. Rahman asked the group whether any of the five supplements have been fulfilled or are far enough along that further detailed discussion is not necessary.

- Dr. Charo suggested that for Recommendation 12A ("Design health record systems to link mother and infant records"), the designing of the systems appears to be well underway but the coordination and convergence of systems needs work because of the inability to share information across systems. Many different tools have been developed to create linkages, but they cannot be aggregated. She also asked whether state hygiene collections of newborn blood spots are available for DNA testing to aid in linkages, suggesting the lack of information on this topic is reason to classify this activity as requiring additional attention/consideration. Jennita Reefhuis, Ph.D., said that CDC is still years away from getting blood spot samples into any centralized system. Dr. Rahman said in light of the need for more discussion, Dr. Charo's blood spot recommendation

should be tabled. Dr. Bucci-Rechtweg noted that Recommendation 12A has three subcomponents. These do not have to be completed; the question is whether action has been taken on them. Interoperability, or ability to speak between systems, may still require additional focus.

- Dr. Nachman addressed 12C ("Use novel data resources"), saying that the development (e.g., grants, contracts) pathway seems to be working with some creative solutions proposed. This supplement is not fulfilled, but it is ongoing,
- Dr. Rahman asked for a general endorsement for the two subcomponents of 12C ("Support large post-marketing observational studies to evaluate the safety and effectiveness of medication classes during pregnancy and lactation" and "Support studies across multiple drugs using the same infrastructure to conserve resources"). Group members said that these subcomponents are ongoing, with the exception of evaluating the effectiveness of medications. The concern was that, despite being ongoing, the implementation is not really getting to the point of some of the things in the recommendation, such as effectiveness. More discussion is required about Recommendation 12C.
- Dr. Rahman asked whether the group found that Recommendation 12E ("Require common data elements (CDEs) to facilitate collaboration") was far enough along to require no significant discussion about what is fulfilled or planned. Is there any meaningful conversation that needs to occur about CDEs, or is there enough direction that additional conversation from this group would not be necessary? It was noted that all policy takes years to implement and that not all of these recommendations will be "actioned" by the time the report is made to Congress. Many of the recommendations are complex, and most will either be ongoing, be planned, or require additional reconsideration. To consider a recommendation fulfilled would mean that all the actions needed to see it come to light are done.

Dr. Rahman said that she was not hearing endorsements for any of the recommendations, indicating that more discussion is required. An attendee said the group should hear from other entities and speakers in order to make a full determination about progress. It was noted that the group has heard from speakers from agencies across the government. The report to Congress can specify what progress has been made from the specific agencies that presented to the group. The report would be a reflection of the requisite actions taken by the responsible agencies. Dr. Charo suggested that the report separate pregnancy and lactation in the recommendations and deal with the progress of each separately, because lactation-related measures have not made sufficient progress. An attendee suggested that the issue of AI is a key missing element from the discussion of registries, especially when considering large data manipulation or modeling. A computer scientist might be a helpful addition to the group. Other attendees noted that there are significant limitations and privacy concerns with certain AI tools.

Dr. Rahman asked the group to systematically evaluate Recommendations 12 and 13 and their supplements in terms of how well they have been addressed and whether more information is needed (the group agreed that lactation should be identified as deficient in all areas unless specifically noted otherwise):

- 12A: The group agreed that there has been movement in this space for pregnancy, but more work is required. Dr. Hardy noted that work that has been done on databases and linkages in the pharmacoepidemiological world has suffered from the inability to cross-talk and suggested the need for sharing methods. Comments from the chat included taking a "watch and wait" approach to this supplement, noting that the lack of patient-reported

outcomes in most registries is problematic; broadening linkage with outside institutions; determining whether there is ever a linkage of one mother with multiple births; suggesting the need for further expansion of large health systems; identifying which populations might be missing due to the types of datasets (e.g., home births); and agreeing that standardization of data across all systems is essential.

- 12B: The group agreed that this recommendation is ongoing for pregnancy, but a more detailed elucidation of specific barriers and limitations is needed before implementation is possible. Group members noted the concerns raised by the FDA speakers about who owns the data. Dr. Charo said that different data sources have different areas of bias (e.g., whether a source includes underrepresented populations), so an evaluation of data sources is needed to gauge whether they are accurate snapshots. Other concerns included the fact that large databases are proprietary and can be expensive or difficult to access, the need for more information about duplication across datasets, and the need for transparency for both data and the methods used to accumulate the data. Group members asked whether there is a website that provides a list of registries and other resources and whether the NICHD DASH website would be helpful for this. Dr. Vance said that DASH will only point users to deidentified data in the DASH repository, but discussions are ongoing about how to facilitate identifying data—particularly reproductive health data—across repositories, not just within DASH. Dr. Vance said the MPRINT knowledge portal should eventually be a helpful tool for finding data. There is a need to be able to find data, because data are currently being shared and stored in so many different places. Dr. Rahman summarized that the group considers this recommendation ongoing, but there may be accessibility and transparency issues to be addressed.
- 12C: The group noted that movement is occurring in the safety—but not the effectiveness—space. Dr. Bucci-Rechtweg suggested that because effectiveness is an essential component, the report should discuss the ability to measure effectiveness with the current tools and whether additional tools are needed for effectiveness analyses.
- 12D: The group agreed there was some movement in this area, but the activity and the group's knowledge of the activity are incomplete. A member suggested that the methods of data analysis presented at this meeting were working well but were not novel or innovative as prescribed in the Recommendation. A member noted that for 12D(b) ("Use data analytics methods to link multiple data sources"), evidence that there are at least pilot data showing that this capability is ongoing was presented. One member was concerned with the lack of public–private partnerships to promote innovative methods and suggested this area might be coded red. Dr. Vance cited the NICHD Transitional Research PAR using novel analytics such as AI, ML, and natural language as a tool to drive interest in this area in the research community. Dr. Rahman said that this funding opportunity lays the foundation for realizing this particular recommendation, even if the fruition might be years in the future. Dr. Bucci-Rechtweg suggested that it might be helpful to invite a colleague with expertise in these innovative spaces to provide insight on how advanced these resources currently are and where they can be practically applied. An attendee suggested adjusting some of the methods developed in other areas to pregnancy and wondered whether there might be publications or presentations about such a process. The group agreed that subpart 12D is the least far along.
- 12E: The group agreed that this subpart shows movement, but it was noted that CDEs across EHRs are not well advanced, and CDEs and data dictionaries are not available for many studies, so there is still a long way to go before this can be "required." More information is also needed about patient-reported outcomes.

Dr. Bucci-Rechtweg moderated the discussion for Recommendation 13. She said that because time was running short, any supplements not discussed at this meeting would be addressed by the group at a later date. Dr. Bucci-Rechtweg asked the group to keep the word “optimize” in mind during this discussion of the recommendation supplements.

- 13A: Ms. Tetlow said she was leaning toward not started or needs additional attention because there are such significant barriers to implementation of this supplement. Ms. Schubert said the recommendation needs much more conversation about optimization, and other group members agreed. Dr. Bucci-Rechtweg asked for thoughts about 13A(b), which calls for a public–private partnership to host a pregnancy or lactation registry. Consideration is needed about who is responsible for convening this public–private partnership. The group discussed the APR, noting that it was chosen as a model because of its depth of history, wealth of information, and multi-stakeholder perspective. Submissions are entirely voluntary. The APR’s unique value is that it is disease-based, uses well-established methods for collecting data, and allows for comparison of exposures early in the pregnancy. It is successful both in terms of collaboration and in being straightforward for pregnant people to participate. An attendee suggested that the biggest problem in developing registries is the lack of incentive for people to submit data to them. Aaron Pawlyk, Ph.D., explained that NICHD began curating the LactMed registry 3 years ago, and the National Library of Medicine hosts the web-based platform and database. There are currently no private contributions. He asked for opinions from the group about what the next iteration of LactMed should look like, since NICHD is in the process of reviewing it. The group agreed that the lack of lactation information in registries means that item needs more attention.

Dr. Bucci-Rechtweg thanked the participants and said she would arrange a date to review the rest of the Recommendation 13 supplements. She acknowledged the significant amount of information the group must cover in a relatively short period and asked for any suggestions about different ways to do so.

Dr. Carpenter said more information would be forthcoming about addressing the NICHD Council in June 2024.

Dr. Rahman asked the group to contact her with suggestions for speakers to provide insight about the recommendations that will be addressed at the next meeting on January 19, 2024.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Task Force on Research Specific to Pregnant Women and Lactating Women Implementation Working Group of Council

MEETING 2 MINUTES

January 19, 2024 (Virtual)

Working Group members present:

- **Rebecca Abbott**, Society for Maternal-Fetal Medicine
- **Susan Abdel-Rahman, Pharm.D.**, Health Data Synthesis Institute
- **Allison August, M.D.**, Comanche Biopharma
- **Pamela Berens, M.D., FACOG**, University of Texas Health Science Center at Houston
- **Christina Bucci-Rechtweg, M.D.**, Novartis Pharmaceuticals Corporation
- **Christina Chambers, Ph.D.**, University of California, San Diego
- **R. Alta Charo, J.D.**, University of Wisconsin–Madison
- **Rebecca Clifton, Ph.D.**, Milken Institute School of Public Health, The George Washington University
- **Alison Cowan, M.D.**, Mirvie
- **Anthony DeLise, Ph.D.**, Novartis Pharmaceuticals Corporation
- **Camille Fabiyi, Ph.D., M.P.H.**, NICHD
- **Elena Gorodetsky, M.D., Ph.D.**, NIH
- **Julie Grimes, IBCLC, RLC**, Lactation Education Resources
- **Janet Hardy, Ph.D., M.Sc.**, Independent Consultant
- **Alison Harrill, Ph.D.**, U.S. Environmental Protection Agency
- **Kenneth (KJ) Hertz**, March of Dimes
- **Elisa A. Hurley, Ph.D.**, Consultant, Bioethics and Human Subjects Research
- **Yasaswi Kislovskiy, M.D., M.Sc.**, Drexel University College of Medicine
- **Sharon Nachman, M.D.**, State University of New York at Stony Brook
- **Sara Quinney, Pharm.D., Ph.D.**, Indiana University School of Medicine
- **Jennita Reefhuis, Ph.D.**, Centers for Disease Control and Prevention
- **Kathryn Schubert, M.P.P., CAE**, Society for Women's Health Research
- **Rachel Gandell Tetlow**, American College of Obstetricians and Gynecologists
- **Eleni Tsigas**, Preeclampsia Foundation
- **Jasmina Varagic, M.D., Ph.D., FAHA**, National Heart, Lung, and Blood Institute
- **Kaveeta Vasisht, M.D., Pharm.D.**, U.S. Food and Drug Administration
- **Kevin Watt, M.D., Ph.D.**, Spencer Fox Eccles School of Medicine, University of Utah
- **Lynn Yee, M.D., M.P.H.**, Northwestern University Feinberg School of Medicine

Opening Remarks

Emma Carpenter, Ph.D., M.S.W., Health Policy Analyst, NICHD

Dr. Carpenter welcomed the PRGLAC Working Group (WG) of Council members and described the meeting logistics.

Meeting Overview

Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation, and Sue Rahman, Pharm.D., American Society for Clinical Pharmacology & Therapeutics, Co-Chairs

Dr. Bucci-Rechtweg reviewed the results of the PRGLAC WG meeting of November 17, 2023, at which the group reviewed Recommendation 12 ("Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant women and lactating women") and Recommendation 13 ("Optimize registries for pregnancy and lactation"). The group determined that for pregnancy, good progress had been made on Recommendation 12, and although work remains to be done on Recommendation 13, progress is being made there too. However, for lactation, progress is less advanced, and more work is required for implementing these two recommendations for patients who may need medications during lactation. Dr. Bucci-Rechtweg cited the PRGLAC WG's charge from Congress to "monitor and report on implementing recommendations, updating regulations, and guidance, as applicable, regarding the inclusion of pregnant women and lactating women in clinical trials," noting that it will take time for all of the recommendations to be fully implemented. She also reviewed the PRGLAC WG's specific objectives, which include inviting speakers from federal and nonfederal agencies to discuss progress on the recommendations and identifying both additional work that may be required to implement the recommendations and barriers to implementation. The PRGLAC WG will submit its findings in a report to Congress.

Dr. Rahman reviewed the clusters to be discussed at this meeting:

- Cluster A ("Conduct clinical research trials") and Cluster E ("Novel drug discovery and development"), which include Recommendation 2 ("Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women"), Recommendation 8 ("Develop separate programs to study therapeutic products used off-patient in pregnant women and lactating women using the NIH BPCA as a model"), Recommendation 9 ("Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnancy women and lactating women"), and Recommendation 11 ("Leverage established and support new infrastructures/collaborations to perform research in pregnant women and lactating women")
- Cluster C ("Policy, regulatory, and liability"), which includes Recommendation 1 ("Integrate pregnant women and lactating women in the clinical research agenda"), Recommendation 4 ("Remove regulatory barriers to research in pregnant women"), 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"), and Recommendation 10 ("Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research")

Session I: Recommendations in Clusters A and E (Clinical Trials/Drug Development)

Presentation 1: Leveraging Clinical Trial Networks for Advancing Therapeutics in Pregnancy

Nahida Chakhtoura, M.D., M.S.G.H., Branch Chief, Pregnancy and Perinatology Branch, NICHD

The Pregnancy and Perinatology Branch includes three networks: the Maternal-Fetal Medicine Units (MFMU) Network, the Neonatal Research Network (NRN), and the Global Network for Women's and Children's Health Research (Global Network). These decades-old networks have recently been modified to increase the award duration from 5 to 7 years, enhance the rigor and reproducibility of clinical trial protocols, promote greater availability of multisite clinical trial infrastructure, facilitate data sharing and access to biospecimens, and enable greater involvement of diverse populations. These networks were recompeted in the past year, with an infrastructure consisting of a data coordinating center and clinical sites. Clinical trial protocols will be submitted through a separate grant application process via a funding opportunity released in November 2022. The upcoming funding cycle for new clinical trials is 2023–2030.

Dr. Chakhtoura discussed two of the three branch networks. The MFMU Network is designed to reduce maternal, fetal, and infant mortality and morbidity. Its focus is on preterm birth, fetal growth abnormalities, and maternal complications. The goal is to expand the evidence base around the safety and efficacy of therapeutic treatment used during pregnancy and lactation by conducting rigorous and reproducible multisite clinical trials and observational studies. The 14 clinical sites, spread geographically across the country, have had a significant impact on clinical practice, with more than 25% of papers cited in medical guidelines. An example of a significant paper is Tranexamic acid to prevent obstetrical hemorrhage after cesarean delivery (*New England Journal of Medicine*), which concluded that prophylactic use of tranexamic acid during cesarean delivery did not lead to a significantly lower risk of a composite outcome of maternal death or blood transfusion than placebo. Dr. Chakhtoura also noted how a National Heath, Lung, and Blood Institute (NHLBI)–funded study established in 2013 to look at long-term adverse pregnancy outcomes was able to study 6,000 participants enrolled in the original 2010 NICHD-funded Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), an example of successfully leveraging a primary study for a secondary study affecting clinical practice.

The Global Network is designed to improve maternal and child survival by focusing on high-need areas such as preventing and/or treating obstetrical complications, modifying childbirth practices, improving infant birth weight and nutrition, and reducing complications from preterm delivery in rural areas globally. Studies are supported by the Foundation for NIH (FNIH) and other entities. Scientists in developing countries team with peers in the United States to address the priorities and needs of the research areas in low-resource centers, mainly in Africa and Asia. Examples of Global Network studies include the Azithromycin Prevention in Labor Use Study (A-PLUS), designed to reduce maternal infection. A-PLUS found that single-dose azithromycin can reduce the risk of postpartum sepsis and death by one third; the trial was stopped for efficacy because of this maternal benefit, and the recent Prevention of Iron Deficiency Anemia Post-Delivery trial, which is enrolling participants in order to assess the efficacy of a single infusion of intravenous iron compared with the standard dose of elemental iron taken twice daily for 6 weeks. Dr. Chakhtoura added that all of these trials go into the NIH Data and Specimen Hub.

Discussion with Dr. Chakhtoura

Rachel Tetlow asked what work the MFMU Network has been doing specific to therapeutics. Dr. Chakhtoura said she would provide a list of that work.

Alison August, M.D., asked for information on conventional trials in pregnant patients. Dr. Chakhtoura said that there are trials that have been conducted through the network, such as the tranexamic acid study, and she would provide a list of trials to the WG.

Eleni Tsigas, noting that the networks have been in existence for decades, asked whether the networks have incorporated any of the PRGLAC recommendations and what changes have been made as a result. Dr. Chakhtoura said these networks have been at the forefront of improving maternal health for PRGLAC, but there are always roadblocks. The new network structure should allow for more cross-network collaborations, with enhanced sharing of biospecimens and increased therapeutic information from the clinical trials. Rebecca Abbott said it would be helpful to hear more about the roadblocks at some point.

Presentation 2: Catalyzing Innovation in Maternal Therapeutics: Novel Networks and Drugs

Aaron Pawlyk, Ph.D., Branch Chief, Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), NICHD

Dr. Pawlyk discussed the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub as it relates to new approaches being taken as a follow-up to PRGLAC activities and the ability to catalyze innovation in maternal therapeutics for pregnancy and lactation. The MPRINT Hub is a service center and scientific catalyst designed to provide knowledge and expertise to the scientific community, catalyze and accelerate maternal and pediatric therapeutics toward precision medicine, synergize with other resources and networks, and build upon current and prior OPPTB efforts. Dr. Pawlyk described the work of the MPRINT Knowledge and Research Coordination Center (KRCC), awarded to Indiana University and the Ohio State University, that includes a number of critical cores. The Knowledgebase & Portal Core extracts usable information related to maternal and pediatric therapeutics and puts it into a broader ontological framework that can be mapped to various types of data (e.g., electronic health records [EHRs], drug ontologies) to better inform therapeutic trials. The Real-World Evidence Core uses mother–baby linkages to better characterize maternal and pediatric drugs by combining EHR data with biospecimens and other types of data. The Pharmacometrics and Clinical Trial Design Core designs pharmacometric models supporting clinical trial design. The Outreach and Dissemination Core focuses on the Hub website, research dissemination, and education and training. The overall goal is to better design trial studies by modeling informed drug development and trial design.

Dr. Pawlyk described the work of some of the MPRINT Centers of Excellence. The Vanderbilt Integrated Center of Excellence in Maternal and Pediatric Precision Therapeutics (VICE-MPRINT) focuses on projects related to pharmacogenomics and outcomes of maternal and neonatal opioid use, as well as providing a precision therapeutics academy for education, teaching, and training that is linked with other training activities across NICHD. The MPRINT Center for Excellence in Therapeutics at the University of California, San Diego (UCSD) focuses on the pharmacokinetics (PK) of antibiotic use in mothers and breastfed infants, as well as projects analyzing the metabolome in human milk and modeling drug effects. Dr. Pawlyk noted that UCSD recently created the Human Milk Institute (HMI) as a central hub to advance human

milk research, from molecular discoveries to local and global public health impacts. The MPRINT Center of Excellence in Therapeutics is one of the many programs under the HMI umbrella.

Dr. Pawlyk discussed the Collaborative Online Perinatal & PEdiatric Repository (COPPER), funded through the MPRINT Hub, with the goal of characterizing pregnancy biobanks to determine the availability of biospecimens for research on preeclampsia and other adverse pregnancy outcomes. This unique approach leverages extensive numbers of biosamples.

Another MPRINT collaboration, this one with the Biomedical Advanced Research and Development Authority, resulted in the initiation of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), which looks at COVID-19 vaccines in pregnancy, to track the effects and outcomes of vaccines and medications in pregnancy. VAMPSS has completed enrollment of 2,500 participants for the first two aims and captured pregnancy outcomes for 1,800 participants. Enrollment toward a third aim, to look at immune response, is ongoing.

Dr. Pawlyk described two MPRINT Hub funding opportunities: the KRCC Opportunity Pool, designed to support projects that address emergent needs and leverage novel technologies in maternal and pediatric therapeutics, and the Centers of Excellence Support Pools, designed to fund innovative pilot or feasibility studies or studies that address emerging needs or gaps in ongoing MPRINT projects. Requests for information should go to info@mprint.org. Dr. Pawlyk showed the funding of awards from KRCC, the VICE Support Pool, and the UCSD Support Pool, noting that the many awards have gone to clinical and postdoctoral fellows and junior faculty, with a good division between pediatric, pregnancy, and lactation research.

Dr. Pawlyk next discussed what is being done in the area of novel drugs for obstetric and lactation conditions, noting that less is being done with lactation. Novel therapeutics require qualified biomarkers for patient stratification, improved nonclinical safety, and drug target validation.

Work on qualified biomarkers has been enhanced by FNIH, an independent nonprofit organization chartered by Congress to support NIH's mission. FNIH establishes various partnerships that NIH, as a federal agency, is not permitted to create. One of these partnerships is the Biomarkers Consortium (BC), which funds projects that bridge the gap between basic research and practical needs for advancing drug development and regulatory science. The BC counts advancing 14 therapeutics, nine drug development clinical tools, and the Biomarker Evidence Criteria and Framework Guidance among its achievements. The BC has also established a public–private partnership to propel early diagnosis and drug development in preeclampsia by leveraging existing cohorts, commercial kits contributed by diagnostic companies, and academic collaborators to generate data from existing angiogenic biomarkers. These data could be used in regulatory filings on qualified biomarkers for future drug development studies and clinical treatment of high-risk patients. The real endgame of this project is the development of a new algorithm for calculating preeclampsia risk in the United States.

A new component of the MPRINT Hub, Developing Extracellular Vesicle-Based MPRINT Translational Resource Platform for Monitoring Therapeutics Response During Pregnancy, is a biomarker platform for placental and fetal exosomes. Exosomes are extracellular vesicles that are good representations of the physiological status of the original cell. Because a pregnant person's blood contains about 30% of placental exosomes by the third trimester, these exosomes are a great source for potential biomarkers. Proteomics of circulating placental exosomes have shown differences between normal and preterm pregnancies. Dr. Pawlyk noted

that a registration site for a workshop on building a maternal health innovation knowledge resource will soon be available. Co-organized by NICHD, MPRINT, and FNIH, the workshop, scheduled to be held on May 6 in Bethesda, Maryland, will feature a wide variety of participants discussing how to obtain more types of biomarkers and use them more effectively (e.g., by interfacing with existing databases).

Improving nonclinical safety requires novel models to assess safety and efficacy during pregnancy and lactation. Dr. Pawlyk highlighted three projects being funded by NICHD:

- Developing extracellular vesicle-based therapeutics for pre-term birth using maternal-fetal interface chips (Principal Investigators [PIs] Arum Han and Ram Menon)
- *In vitro*, *in silico* placental barrier model for predicting fetal exposure and toxicity (PI Carrie German)
- Placental organoids to assess therapeutics for preeclampsia (PI Ananth Karumanchi)

NIH is also planning a Common Fund research program, the Complement Animal Research in Experimentation (Complement-ARIE) program, to catalyze the development, standardization, validation, and use of new approach methodologies. The program has the potential to change the landscape of available regulatory tools, and pregnancy and lactation must be included in this effort.

Dr. Pawlyk concluded by discussing the third requirement for novel obstetric therapeutics: drug target validation. He cited three important projects supported by the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) programs and conducted by three different bioscience companies:

- Therapeutic targeting of FKBP51 for the prevention of stress-induced preterm birth (PI David Friend)
- Therapeutic antibody for hyperemesis gravidarum (PIs Andrew Mendelsohn and James Larrick)
- Novel pharmacological treatment of preeclampsia (PI Mohammad Uddin)

In addition, FNIH has supported working with private partners to understand disease pathways and discover new targets and biomarkers. Work is ongoing to leverage data science and partnerships for disease insights, biomarkers, and drug targets. Dr. Pawlyk likened the process to a pyramid, building on repositories, registries, and data warehouses to develop tools and algorithms that are accessed by the development of knowledge portals (e.g., the Human Genetics Amplifier, the Reproductive System Knowledge Portal) and ultimately leading to new drug targets and biomarkers.

Presentation 3: Progress on Prioritization of Drug, Vaccine, and Dietary Supplement Research Needs for Pregnant, Postpartum, and Lactating Persons

Camille Fabiyi, Ph.D., M.P.H., Program Officer, OPPTB, NICHD

Dr. Fabiyi discussed the progress of the Request for Information (RFI) inviting nominations for the Prioritization of Drug, Vaccine, and Dietary Supplement Research Needs for Pregnant, Postpartum, and Lactating Persons; one of the RFI's goals is to obtain information to advance Recommendations 8b and 9a in the 2018 PRGLAC report and the 2020 PRGLAC implementation plan. The public comment period is over, and 136 nominations were received. The majority of the nominations were for drug research (114), versus vaccines (2) or dietary

supplements (20) and related to general medical conditions (79) versus lactation- (22) or pregnancy- or postpartum-specific research (35). Of the top 10 therapeutic areas indicated in the nominations, preterm birth ranked third (11), and milk supply ranked seventh (8). The nominations are currently being reviewed, stakeholders will be consulted, and NICHD expects to finalize and publish the initial list of prioritized drug, vaccine, and dietary supplement needs in mid- to late 2025.

Discussion with Dr. Fabiyi

Ms. Abbott asked about next steps after the priority list is finalized in 2025. Dr. Fabiyi said the priority list will be used to influence the types of NIH funding opportunities.

Review of the Recommendations That Are the Focus of the Discussion for Clusters A and E

Before opening the floor for a discussion with all the presenters, Dr. Bucci-Rechtweg reviewed the recommendations that are the focus of the discussion for Clusters A and E:

- Recommendation 2: “Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women.”
    - 2A: “Provide additional resources and funding for research to obtain clinically meaningful and relevant data for specific and co-existing conditions in pregnant women and lactating women.”
    - 2B: “Utilize longer award periods by government funders (beyond the typical 5-year award), when needed, for study design and data collection.”
- Recommendation 8: Per the notice to the PRGLAC WG, this recommendation will not be discussed, because there has not been sufficient work toward its implementation, and additional resources or congressional actions are required for this to be actionable.
- Recommendation 9: “Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women.”
    - 9A: “Create separate prioritization processes for pregnant women and lactating women.”
    - 9B: Per the notice to the PRG WG, this sub-recommendation would not be discussed at this meeting, because there has not been sufficient work toward its implementation, and it is the perspective of the chairs that additional resources or congressional actions are required to act upon 9B.
- Recommendation 11: “Leverage established and support new infrastructures/ collaborations to perform research in pregnant women and lactating women.”
    - 11A: “Provide financial support and incentives to [establish] and develop new multicenter infrastructures that capitalize on standard-of-care procedures (opportunistic studies), innovative designs, and methodologies.”
    - 11B: “Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women.”
    - 11C: “Encourage networks/collaborations to engage in public–private partnerships to facilitate research.”

Moderated Discussion on Clusters A and E

Discussion Related to Recommendation 2 and Sub-Recommendations 2A and 2B

Yasaswi Kislovskiy, M.D., M.Sc., asked how the networks are used for lactation studies, how areas of study are prioritized, what mechanisms for transparency are in place for the prioritization processes, and whether there are plans for inclusion of rural areas in the United States into the MFMU Network. Dr. Chakhtoura said that the MFMU Network–funded clinical sites are those that applied to the funding opportunity. Applications for clinical sites and data coordinating centers are reviewed and funded based on availability of funds. Investigators can submit to PAR-23-37 for studies leveraging NICHD networks. The science within the networks is prioritized. Outside researchers interested in lactation studies can also submit applications to the networks. Moreover, NICHD and the National Institute of Allergy and Infectious Diseases co-fund trials related to HIV medications (and, more recently, COVID-19 medications) taken during pregnancy and lactation. The Maternal Health Research Centers of Excellence, which include rural areas and the needs of those communities, were funded through the IMPROVE (Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone) initiative. Dr. Kislovskiy asked whether the networks might perpetuate bias and whether there is an external board that can review these multi-institution collaborations and ensure diversity of institutions and investigators and inclusion of patients. Dr. Pawlyk provided a link to a description of the preapproval process.

Sharon Nachman, M.D., suggested that it would be important to map where all the sites are. Sites do not appear to be collaborating across networks, either among investigators or with samples, data, and repositories. These sites have been in existence for a decade, and understanding how the sites communicate with one another would be important. Dr. Nachman agreed with the move from a 5-year award to a 7-year award but said that the bigger problem is that the networks are siloed instead of being put under one umbrella, with sites encouraged to work across networks. Dr. Chakhtoura noted that expertise within networks varies, but she agreed about the need for cross-network collaborations and the idea of developing a footprint map of all the networks. She suggested that the collaborative process might be accelerated with the opportunity to open the networks to outside investigators, adding that combining the research sites is not necessary, but being mindful of which regions or institutions are already being funded is. She agreed that the 7-year award period, which cycles from 2023 to 2030 for the MFMU Network, the NRN, and the Global Network, is an improvement. The hope is to extend this longer award time to other networks in the future. Christina Chambers, Ph.D., suggested thinking about the kind of mapping that overlays networks and incentivizes collaborations across networks by providing additional resources to accelerate research initiatives for pregnancy and lactation that benefit from cross-network collaboration (e.g., a collaboration between the NRN and the MFMU Network).

Dr. Nachman asked whether there would now be a clearinghouse for investigators to see science questions or specific clinical trials suggested by the networks. Dr. Chakhtoura said that the investigators, not NICHD, propose the trials. However, consideration is being given to how to address situations where a particular study is funded and then additional resources are needed. Janet Hardy, Ph.D., M.Sc., noting that investigators initiate the research proposals, asked whether it would be beneficial for networks to establish priorities for proposals that would align with PRGLAC and be more directive about the research. Dr. Chakhtoura said that it is a matter of balancing what the expert investigators think is a research priority with what NICHD suggests that the investigators do. She noted that when additional COVID-19 funds were available, NICHD asked the networks what to do, and they responded with a proposal. These kinds of opportunities

arise occasionally, especially when additional funds become available, but the networks' main activities and priorities are led by the experts in the field who are part of the various networks. Dr. Pawlyk provided a link on catalyzing the development and use of novel alternative methods to advance biomedical research. Dr. Nachman noted the fine line between company interest and investigator-initiated studies and emphasized the need for transparency and ensuring that sites that get funding from NICHD actually can participate in other network studies, even ones that are not on the list of chosen sites. Dr. Chakhtoura said there is interest in pursuing more public–private partnerships.

Anthony DeLise, Ph.D., asked about the need for new or modified preclinical studies. He wondered how they would be used, noting that the pharmaceutical industry is a good fit for implementing some new preclinical models to develop data and help with clinical trials or postmarketing. He asked whether some kind of network for this might be formed. Dr. Pawlyk cited the Complement-ARIE program, which might provide models that are more predictive or complement what is being done with typical animal models. The Complement-ARIE program has representatives from multiple agencies and the pharmaceutical industry providing input on developing better models and better ways to use data. This program could explore complex *in vivo* or *ex vivo* type models, complex cellular constructs, and novel and chemical approaches. The Complement-ARIE trans-agency working group is engaging with FNIH and other foundations and institutes to transform the nonclinical space, including for reproductive studies. It is possible these models could be used earlier in the drug discovery phase to identify and eliminate properties in therapeutics that are harmful in pregnancy. Ms. Tsigas wondered how to assess how the longer study periods and new technologies affect the research field in general, asking how many researchers can actually do preclinical safety trials that would lead to including pregnant and lactating women. Dr. Pawlyk provided a link describing the program's strategic planning.

Julie Grimes said that more information about barriers to lactation therapeutic studies is needed. One safety measure for lactation studies would be to look at the pharmacokinetics, specifically daltons and protein binding. Dr. Pawlyk provided a link to a large study looking at pharmacokinetics for drugs commonly used in lactation.

Lynn Yee, M.D., M.P.H., suggested considering pipeline development and funding K awards for faculty working on PRGLAC priorities. Dr. Kislovskiy agreed, noting that the Recommendation 2 implementation plan mentioned the multiple Clinical and Translational Science Award sites as an opportunity, and she suggested changing the mentorship effort required for K awards to support more PRGLAC priority research and encourage early-stage investigators and training centers in this area. Dr. Yee added that NICHD involvement in K24 mechanisms might be another way to expand mentorship and support for early-career PRGLAC investigators. Dr. Pawlyk provided a link about NICHD's training and career development approaches.

Jasmina Varagic, M.D., Ph.D., said that the NHLBI-funded chronic hypertension and pregnancy trial showed that antihypertensive treatment of pregnant women with chronic hypertension to the level of blood pressure targeted in the nonpregnant population is safe and could reduce the incidence of pulmonary embolisms. These results changed the guideline of treatment of blood pressure in pregnant women with chronic hypertension.

Pamela Berens, M.D., asked whether there might be a way to incentivize researchers from the networks who are looking at pregnancy to include relevant lactation research. She wondered whether there was any lactation research exploring how drugs might regulate the milk supply,

either up or down. Dr. Chakhtoura offered to provide more information about a relevant 2018 RFI that had catalyzed the clinical trial network changes. Ms. Grimes suggested that studies looking at insulin's effects on lactation among people with obesity and/or diabetes might also be helpful. Dr. Pawlyk noted that the MPRINT Hub is one of the few groups looking at drug effects on milk quality and supply, and he suggested that more attention be given to this area, perhaps in the biomarker development space. Sara Quinney, Pharm.D., Ph.D., said that breastfeeding and lactation are not well captured in clinical records, even at a single point in time. Alison Harrill, Ph.D., wondered about using duration of breastfeeding (number of weeks) as a surrogate for exposure effect on milk production if these data could be captured by the physician. Jennita Reefhuis, M.D., cautioned that population-based studies on lactation will require considerable work on study designs. Dr. Berens agreed that lactation studies are complicated, often because of mixed feeding, which is not well captured in EHRs. She said getting a full picture requires capturing the amount of breastfeeding, amount of supplementation, and infant growth.

Kenneth Hertz, referring to the Priority List of Drug, Vaccine, and Dietary Supplement Research Needs for Pregnant, Postpartum, and Lactating Persons research, asked what the criteria for the selected conditions and therapies to be chosen first would be, in terms of prevalence, need for study data, and number of studies needed. He also asked about the funding source for supporting this program on an ongoing basis. Dr. Fabiyi said the criteria being considered include evidence (the level of evidence and current therapeutic gaps), impact (the severity of the condition and the number of pregnant, postpartum, and lactating women affected), population (the diversity and range of affected women), and feasibility (resources available to conduct the study and implement findings). Existing NICHD operational funds are supporting the current work.

Ms. Tsigas suggested that much of the translational work will also require input from patient organizations and patient family influencers.

Discussion Related to Recommendation 8

Dr. Bucci-Rechtweg noted that although this recommendation would not be formally discussed at this meeting, Dr. Fabiyi's presentation made clear that NICHD has made progress on prioritization as defined in Sub-Recommendation 8B ("Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women"). Additional work is required for Recommendation 8, particularly as it relates to Sub-Recommendation 8A ("Provide specific funding").

Discussion Related to Recommendation 9

Dr. Bucci-Rechtweg noted that Dr. Fabiyi's presentation also addressed Sub-Recommendation 9A ("Create separate prioritization processes for pregnant women and lactating women").

Ms. Tsigas suggested an offline meeting to better understand what additional resources or congressional actions are required for implementation of Sub-Recommendation 9B ("Consider a Biomedical Advanced Research and Development Authority (BARDA)-like model and the NIH vaccine model that takes clinical development up to phase II"). This would be particularly helpful for PRGLAC members involved in advocacy work. Dr. Bucci-Rechtweg said that additional financial or legislative resources to put activities like a BARDA-like model into place and make them sustainable are likely to be needed, and these policy considerations would be made clear in the PRGLAC WG's report to Congress.

Discussion Related to Recommendation 11

Dr. Bucci-Rechtweg said that although Sub-Recommendation 11A ("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") would not be formally discussed at this meeting, because there has not been sufficient work toward its implementation, the presentations suggest that some work is ongoing, so this sub-recommendation could be included in the discussion. Discussion would ensue on Sub-Recommendations 11B ("Broaden focus of ongoing research networks to include research on therapeutic products in pregnant women and lactating women") and 11C ("Encourage networks/collaborations to engage in public-private partnerships to facilitate research").

Dr. Chambers reiterated her earlier point about incentivizing cross-network collaborations by providing additional resources where an infrastructure already exists.

Dr. Nachman wondered about metrics for success in the individual sites and how those metrics would be used to bring in new sites. For example, if a network study takes 4 years to enroll, are the data current enough to be useful? She suggested the need for a common set of metrics across the networks and sites so that evaluations about whether more sites are needed or investigators should go outside their networks can be made. Having metrics that apply to everyone across all sites would enhance cost-effectiveness and boost all of the networks. Dr. Chakhtoura noted that the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network has 2,630 sites. Investigators can inquire about specific requirements for a protocol, and if IMPAACT has the infrastructure, the investigator can apply. However, for the MFMU Network, the NRN, and the Global Network, the 14 sites that apply have met the minimum requirement, meaning they have the required number of high-risk women able to be enrolled. The expectation is that any protocol that goes out from the networks and is approved by the steering committee would recruit from all sites that are part of the network. Networks might be able to be leveraged for very large studies, but doing so might require additional funds to bring on sites that are not part of the networks with infrastructure provided by NIH. There have been occasions when, because of poor enrollment at the MFMU site, sites were added from the IMPAACT Network, but that raises the question of managing the additional costs of bringing on sites that NIH does not provide infrastructure for. Dr. Nachman said that it would be important for the next generation to consider how to do things better in terms of time and who is tracking how long enrollment takes. Dr. Chakhtoura agreed but noted that the issues Dr. Nachman raises are being taken into consideration and that discussions about partnering with other networks do occur. NICHD has experience with bringing on sites that do not currently receive NIH infrastructure support, and doing so merits further consideration, although it could involve the need for additional resources.

Dr. Bucci-Rechtweg asked the group to think about what it will take to expand networks, foster public–private partnerships, and better incorporate different stakeholder groups that could facilitate bringing new therapeutics to clinical development.

Dr. Chambers suggested that there is great opportunity for public–private partnerships, especially for lactation. She asked what proactive efforts are being made to help educate public and private entities about establishing these kinds of research collaborations.

Dr. DeLise described the European ConcepTION, an Innovative Medicines Initiative (IMI), which is working to identify an alternative preclinical model (e.g., a mini-pig) to explore drug transfer

through the milk via lactation. This mini-pig's milk composition is very similar to human milk, and data from the pig may be translatable to existing human data. The study will also use *in vitro* models to look at permeability coefficients of drugs to help predict infants' drug exposure through nursing. If the data are strong enough, it might be possible to get a qualification opinion. Dr. Bucci-Rechtweg added that this study has public- and private-sector funding and is entirely dedicated to lactation studies. She asked about the factors that led the private sector to get involved. Dr. DeLise said the project started as a preclinical project but quickly attracted private and public partners, perhaps in part because it is trying to address the data gaps for the lactation aspect of labels when developing drugs that could be transferred to the offspring via the milk.

Dr. Bucci-Rechtweg asked Dr. Pawlyk for thoughts on how to expand opportunities for public–private partnerships. Dr. Pawlyk said FNIH is very interested in expanding its efforts in maternal health. One of the challenges in engaging private companies in pregnancy and lactation research is finding champions within the companies who will speak up. However, there may be great opportunities ahead when Complement-ARIE launches and with some of the European programs. Building a coalition of individuals who represent companies and are willing to engage in creating these public–private partnerships will be key.

Kaveeta Vasisht, M.D., Pharm.D., noting previous discussion about the challenges of registries, suggested that this area provides an opportunity for collaborations in public–private partnerships.

Lynne Yao, M.D., suggested tapping into existing groups such as Critical Path Institute as a way to bring people together or creating a platform or space where anyone interested in the idea of a disease-based registry could contribute. She suggested putting forward a recommendation to create a disease-based registry, adding that using models like IMI is doing is on target.

Dr. Pawlyk suggested research looking at the effect of ingested medication on human milk, both in terms of changes to milk composition and in terms of either increasing or decreasing the milk supply. Little work is being done in this area outside of MPRINT, and developing a biomarker for assessing milk quality and level would be beneficial. Dr. Pawlyk also noted the dearth of applications to study therapeutics related to lactation and suggested that more information about why this area is not moving forward is needed. He wondered whether the lack of progress might be due to the difficulty in capturing lactation issues and data. The lack of studies on lactation may be one of the barriers to moving toward target validation. Dr. Chakhtoura added that NICHD is asking investigators who are proposing projects that leverage networks about using innovative designs.

Jennita Reefhuis, Ph.D., suggested using case control studies to investigate lactation or lack of milk production. For situations with women who suffered birth defects or stillbirths, there is a potential for case controls looking at medication use in pregnancy. Dr. Hardy noted that capturing adequate information on lactation or breastfeeding is difficult because it is such a dynamic process and EHRs are not particularly helpful. Dr. Bucci-Rechtweg said she is hearing that there might be a need for very different trial designs for pregnancy therapeutics studies and lactation therapeutic studies and that this must be made clear in the progress report.

Dr. DeLise suggested, as part of Sub-Recommendation 11B, getting a better understanding of the progress being made in the outreach to partner with industry to enhance the data needed for inclusion of pregnant and lactating women in clinical trials. Dr. Pawlyk said that FNIH is interested in industry partnership and that identifying champions in this sector would also be necessary. He noted that the National Academy of Sciences is conducting a study about medical

legal liability issues, and he suggested that liability is a key component in getting more private-sector engagement, because liability concerns are inhibiting factors. This outreach should be done sooner rather than later.

Dr. Kislovskiy raised a concern about the slow movement toward delivery of drugs that have shown good safety data, saying there seems to be an implicit bias that results in some potentially therapeutic or effective novel drugs being held back. How can the dissemination of these drugs be incentivized, or are liability concerns the issue? Dr. Pawlyk said that factors that might inhibit the movement of drugs into clinical use include legal liability concerns, especially for a pregnant population but also for lactating women, and clinical trial design, which often requires enrolling a large number of participants, thereby increasing the risk of adverse events. He suggested that having biomarkers available to conduct risk stratification would be important for stimulating the translational pipeline.

Session II: Recommendations in Cluster C (Policy and Regulatory)

Review of the Recommendations That Are the Focus of the Discussion for Clusters A and E

Dr. Rahman reviewed the recommendations:

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.” Dr. Rahman said this recommendation was accomplished in 2019.
- 1B: “The Food and Drug Administration (FDA) should harmonize with the Common Rule and remove pregnant women as a vulnerable population.”
- 1C: “The Department of Health and Human Services (HHS) should develop guidance to facilitate the conduct of research in pregnant women and lactating women.” Dr. Rahman noted that this sub-recommendation will be updated, pending a written update from the HHS Office of Human Research Protections (OHRP).

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

Dr. Rahman said that this sub-recommendation would not be discussed at this meeting, because the HHS OHRP written update is pending.

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.”
- 7B: “… consider implementing a targeted incentive program and/or strengthening FDA authority to require clinically relevant data … on pregnant and lactating women to inform dosing and safety.”

Dr. Rahman said that Recommendation 7 would not be discussed at this meeting, because there has not been sufficient work toward its implementation. The chairs feel that additional resources or congressional actions are required to act upon this recommendation.

Recommendation 10: “Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research.”

- 10A: “Investigators and sponsors must specifically justify exclusion in study design.”
- 10B: “Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation.”
- 10C: “Develop a systematic plan on how data for pregnant and lactating women will be obtained in a timely fashion. …”
- 10D: “Develop guidance for IRBs and investigators. …”
- 10E: “Develop a systematic plan for if a woman becomes pregnant in a study. …”

Leyla Sahin, M.D., deputy director for safety in the FDA Center for Drug Evaluation and Research’s Division of Pediatrics and Maternal Health was present for the discussion.

Presentation 1

Kevin A. Prohaska, D.O., Associate Director of Clinical Policy, Office of Clinical Policy and the Commissioner’s Office, and Senior Bioethicist for Adult Research, FDA

Dr. Prohaska discussed the FDA’s actions related to Sub-Recommendation 1B (“[The FDA] should harmonize with the Common Rule and remove pregnant women as a vulnerable population”). He said that the FDA has an ongoing effort to harmonize with both 21 CFR 50 (protection for human subjects) and 21 CFR 56 (IRB regulations). These two regulations are substantially identical to the Common Rule with a few exceptions. Dr. Prohaska said that the WG had been provided with a link to the proposed rules and that public comments had generally been favorable to the removal of pregnant women from the list.

Discussion with Dr. Prohaska

R. Alta Charo, J.D., asked whether there would be any effect on the special rules concerning consent from the father for research that could affect the fetus. Dr. Prohaska said this issue related to 45 CFR 46 Subpart B, which covers additional protection for fetuses. The FDA did not adopt that regulation, so his office is not involved with changing or looking at it. Ms. Charo said that the FDA website makes it appear that the FDA follows the rule despite not adopting it. Dr. Prohaska said a that draft guidance developed in 2008 that refers to Subpart B is currently under revision. He noted that Subpart B is not an FDA regulation. Ms. Charo said that her understanding was that although it is draft guidance, the FDA follows the same policy for this part of the CFR as NIH does. Dr. Prohaska said that it is probably not written as an absolute guidance that must be followed.

Elisa Hurley, Ph.D., asked about the timeline for the release of the FDA harmonized guidelines. Dr. Prohaska said that the guidelines are expected to be completed by the end of this calendar year.

Presentation 2: FDA Update Recommendation 10

Lynne Yao, M.D., Director, Division of Pediatrics and Maternal Health, Center for Drug Evaluation and Research, FDA

Dr. Yao reviewed Recommendation 10 ("Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research") and its sub-recommendations:

- 10A: "Investigators/sponsors must specifically justify exclusion in study design."
- 10B: "Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation."
- 10C: "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."
- 10D: "Develop guidance for IRBs and investigators about the inclusion of pregnant women and lactating women in research."
- 10E: "Develop a systematic plan for if a woman becomes pregnant in a study, to include whether product should continue, if unblinding is necessary, [and] how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information."

In 2018, the FDA published *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*. This guidance, which is currently undergoing review and revision,

- Specifically discusses considerations for inclusion of pregnant individuals in clinical trials (Sub-Recommendation 10D)
- Does not specifically indicate a requirement to justify exclusions (Sub-Recommendation 10A)
- Specifically discusses the collection of PK data during pregnancy (Sub-Recommendation 10B)
- Specifically discusses women who become pregnant while enrolled in a clinical trial, including referencing unblinding and pregnancy outcome data (Sub-Recommendation 10E) [Note: It does not discuss collection of opportunistic data.]

Dr. Yao said that the guidance falls short in two areas: It does not actually recommend that exclusion be specifically justified (Sub-Recommendation 10A), and it does not explicitly mention collecting opportunistic information (Sub-Recommendation 10E).

In 2004, the FDA published a draft of *Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling*. This guidance, which is undergoing substantial revision, specifically discusses study designs to capture PK information pre-pregnancy, during all three trimesters, and postpartum (Sub-Recommendation 10B).

In 2019, the FDA published a draft of *Clinical Lactation Studies: Considerations for Study Design*. This guidance, which is undergoing review and revision,

- Specifically discusses types of lactation studies and collection of PK data based on stages of lactation (Sub-Recommendation 10B)
- Specifically describes situations in which lactation studies should be considered (Sub-Recommendation 10D)

Dr. Yao said this guidance did address the issues in Sub-Recommendations 10B and 10D.

In 2019, the FDA published a draft guidance titled *Postapproval Pregnancy Safety Studies*, which:

- Specifically discussed the types of studies that can be considered to collect postapproval safety data (Sub-Recommendation 10C)
- Does not discuss specifics related to "timeliness," but the FDA framework under the Prescription Drug User Fee Act (PDUFA VII) focuses on optimizing use of postapproval pregnancy safety studies (Sub-Recommendation 10C)

Dr. Yao noted that the FDA's real interest under PDUFA VII is to optimize the use of postapproval safety studies to understand safety when drugs are used during pregnancy. The FDA hopes this framework will improve the process of getting timely information back on the safety of drugs and biological products used during pregnancy. Dr. Yao added that the PDUFA framework focuses on safety, not PK or PD, and noted that the FDA Guidance relating to Sub-Recommendation 10D can be used by IRBs and investigators. Overall, the FDA guidances or frameworks have begun to address all of the sub-recommendations of Recommendation 10 except 10A.

Dr. Yao identified two gaps:

- Sub-Recommendation 10A says, "…authorize the FDA to require drug developers to provide a 'PRGLAC Study Plan' and 'PRGLAC Assessment' during drug development. …" This is repeated in Sub-Recommendation 10C. However, there is currently no explicit statutory or regulatory requirement that sponsors submit a PRGLAC Study Plan.
- The FDA is just one agency working on updates for the PRGLAC recommendations; it cannot speak to what academia, industry, or other governmental agencies may be doing.

Discussion with Drs. Yao, Prohaska, and Sahin

Dr. Nachman asked whether there is a regulatory need for pregnancy studies or some commitment that data from the studies will become part of the package insert. It is common to find that drugs licensed in adults have no data on pregnancy. The question is how to approach pharmaceutical industry to do these studies and understand what the commitment is on the network side when the studies are written to submit the data. Dr. Sahin said that post-marketing requirements (PMRs) are issued at the time of approval, with definite timelines included. When a new drug is approved, there is an approval letter with language that outlines the parameters of the safety studies or lactation studies with milestone dates for completion. Dr. Nachman asked whether every new drug must go through this requirement or whether companies are allowed to opt out and not use the drug during pregnancy. Dr. Sahin said this was a gap area, as Dr. Yao pointed out in her presentation, and showed the need for a systematic plan for pregnancy and lactation studies to understand which studies are needed to address data gaps, as PRGLAC has recommended.

Ms. Charo said there were two different issues: the inclusion of pregnant women in trials and Phase IV study postapproval. She asked what percentage of Phase IV studies are completed or completed on time and what disciplinary measures have ever been taken in terms of occurrences such as having drugs recalled because of black box warnings. Would it be better to focus on preapproval when industry has a strong incentive to get the drug to market? Dr. Yao said that a

recent review of how many pregnancy registries were conducted and how many were successfully fulfilled showed that the registry studies and the data from PMR studies that were completed all used a disease-based type of registry. She acknowledged that PRGLAC WG members had made important points about whether data will be obtained in a timely manner and whether the data would provide information that supports a change to the labeling. Perhaps there should be a focus on premarket. Dr. Yao opined that it will probably take a combination of both pre- and postmarket data, because getting enough from premarket information alone is unlikely to be possible. She agreed that this was an area that could be greatly improved upon.

Ms. Abbott said that, in terms of justifying excluding pregnant women, the advocacy community has worked to ensure that pregnant and lactating people were included in the requirements of the diversity action plans as part of the 2023 omnibus. Dr. Yao agreed that this was a helpful approach. Ms. Charo noted that one of the problems with requiring justification for inclusion but not for exclusion is that it creates a default presumption of exclusion, which becomes a psychological and practical barrier to increasing inclusion.

Dr. Yao said that guidelines she discussed in her presentation are not yet final, so there is still an opportunity to make changes that are more reflective of the PRGLAC recommendations. Dr. Bucci-Rechtweg noted that the focus of the PRGLAC WG is to evaluate the progress of the recommendations and sub-recommendations. She added that the mix of pre- and post-market recommendations generate different types of information that will better inform labeling for use in pregnant and lactating populations.

Ms. Tetlow asked whether, with the completion of Recommendation 1A in 2019, changes in the numbers of research trials that have included pregnant and lactating populations or in IRB approaches have been observed. Ms. Abbott, suggesting that research has not shown a change, provided a link about ongoing gaps. Dr. Prohaska said he was not aware of any data relating to whether more pregnant and lactating women have been included in research as a result of these changes. He has heard anecdotally from IRB members that the sub-recommendations have had an impact on their deliberations. The hope is that removing pregnant women as an example of a vulnerable population will facilitate IRB review and allow more research to go forward. It is not clear whether that will translate into more protocols being submitted to the FDA in this area. Dr. Bucci-Rechtweg suggested doing an assessment of ClinicalTrials.gov, searching specifically for trial inclusion/exclusion criteria, and applying various filters leveraging the NICHD prioritization work. She welcomed suggestions on the use of other databases as well. Ms. Tsigas noted that there is published literature analyzing the exclusion of pregnant women from COVID-19 trials.

Dr. Kislovskiy asked whether pregnant and lactating women are being included in discussions about how research is designed or conducted. She suggested that this should be encouraged, especially by community advisory boards and advocacy groups, and its progress tracked. Dr. August agreed with the importance of including patient advocates' voices from the beginning of the study planning processes, for both the informed consent composition and the protocol itself.

Dr. Prohaska provided a link to the FDA draft guidance.

Discussion of Recommendation 10

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

- 10A: “Investigators/sponsors must specifically justify exclusion in the study design.”
- 10B: “Ensure studies are designed to capture the time dependency of physiologic changes in pregnancy and lactation.”
- 10C: “Develop a systematic plan on how data for pregnant and lactating women will be obtained in a timely fashion. …”
- 10D: “Develop guidance for IRBs and investigators. …”
- 10E: “Develop a systematic plan for if a woman becomes pregnant in a study. …”

Dr. Yao agreed that the PRGLAC WG should track how many pregnant people have been enrolled in clinical trials as a result of the PRGLAC recommendations and FDA guidances, as well as how many registry studies have been completed post-PRGLAC compared with pre-PRGLAC. Dr. Rahman noted that the group seemed to be moving beyond just evaluating progress and toward also evaluating impact.

Dr. Hurley suggested that the importance of Recommendation 10 has not been sufficiently addressed, because so many of the FDA guidances are still in draft form. She emphasized the importance of getting the justification of the exclusion included in the guidance, noting that industry takes FDA guidance. This issue should be included in the report, because the exclusion of pregnant women from trials has become ingrained culturally, and this must change.

Ms. Charo asked whether the role of the marital or nonmarital partner is being addressed in the FDA guidances that are being developed. This might actually affect whether a pregnant woman can even enroll in research. Dr. Prohaska said the current regulations require that the woman give consent. If the protocol involves an unusual risk, the FDA suggests that parents or another family member be part of the thinking process, but it is ultimately the woman’s decision. Ms. Charo recalled being involved in cases in Africa where women would not enroll in studies that were to their benefit for fear of family members learning they were HIV positive. She suggested thinking creatively about how family situations can actually act as barriers to enrollment. Dr. Prohaska agreed, noting that similar issues had arisen in the past during the Ebola crisis.

Dr. Pawlyk observed that NIH currently does not have any inclusion or exclusion requirements regarding pregnancy or lactation in its inclusion policies. There are few tools at NIH to aid tracking inclusion of these populations in clinical trials. Ms. Abbott asked whether there might be a way to make this tracking a regular practice at NIH, perhaps by making tracking a requirement for NIH-funded studies. Dr. Pawlyk said that there have been a variety of NIH workshops related to inclusion across the lifespan, and the WG should review some recommendations that were put forth about including pregnant and lactating women. He noted that there is an inclusion governance committee at NIH that oversees the process and recommended that the PRGLAC WG also look at that. Dr. Pawlyk provided a link to the report on inclusion across the lifespan.

Dr. Rahman found it encouraging that real progress has been made in many areas of Recommendation 10, with a good trajectory moving forward on the sub-recommendations.

Dr. Nachman said that she must deal with both the FDA and the European Medicines Agency (EMA) and asked how the FDA guidance would intersect with the EMA, which is currently going through a similar exercise. Will there be concordance? Dr. Yao said that for pediatrics, different laws and regulations between the FDA and the EMA have caused problems and showed the need for harmonization. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline (ICH E21), a harmonized, global guidance on pregnancy and lactation, is currently being developed by a working group, of which Drs. Sahin

and Vasisht are both members. A group of regulators also regularly meets for discussion, and there is a pregnancy and lactation cluster that has been developed since the PRGLAC recommendations came out, helping ensure that everyone is moving in the same direction. There is great anticipation about the ICH E21 guideline, which will be a roadmap that all regulatory agencies and pharmaceutical groups are part of ICH will commit to adopting. Dr. Bucci-Rechtweg said that this will be a welcome guidance and something the PRGLAC WG report should speak to.

Dr. Bucci-Rechtweg suggested that Sub-Recommendation 10E is important because of the potential to generate information across the trimesters. She asked the group to comment on where some progress might be made in terms of identifying a path forward for what to do if a participant in a routine clinical study becomes pregnant. Dr. Reefhuis suggested assembling a group of experts from industry and academia who conduct these kinds of studies on a regular basis to brainstorm an approach to developing a systematic plan. Dr. Yao found this suggestion to be interesting. She said the FDA might have the statutory authority to require that a systematic plan be developed, but the real opportunity is to collaborate with people who are actually conducting these trials to develop the algorithm describing the data to be collected, the outcome of the pregnancy, and possibly a reconnection to the trial at some point. Dr. Hardy agreed that this was an excellent recommendation, noting that, from an industry standpoint, the people who need to be consulted are the operations people—the ones in charge of the trial—because the plan will require their buy-in. Dr. Bucci-Rechtweg suggested that if a pregnant woman with an underlying medical condition is doing better on her medication, her baby will also do better. People in the clinical development space would appreciate guidance from experts on how to proceed, and it is likely that many experts would be eager to participate in such a discussion.

Dr. Vasisht recalled that some industry representatives did not agree with the sub-recommendations of Recommendation 10, and she suggested finding out whether this thinking has evolved. Dr. Bucci-Rechtweg said that those concerns occurred early in the process, when some recommendations that appeared in the final document had not been discussed in the task force. However, after robust discussion, there are now clear elements that agency and industry are completely aligned with.

Ms. Charo noted that liability exposure is mentioned in Recommendation 7, and she emphasized the importance of making a distinction between the perception about liability and the reality, because the reality is that there has been a great deal of liability, but it is mainly in the context of drugs that were not studied in pregnant women, not due to enrollment of pregnant women in a clinical trial. There are so few data in these cases that when they come before a judge or a jury, there is great unpredictability, which leads to a culture of presumptive exclusion of pregnant women. Liability should not be considered a major threat when it comes to enrollment, because enrollment is a controlled situation where there is an opportunity to decide the level of risk, minimize it, and counsel the person about the risk. The real liability risk comes from not testing on pregnant women before selling the drug, and this has resulted in findings of liability. Ms. Charo was concerned that Recommendation 7 was buying into an assumption about underlying liability that is not empirically justified. Dr. Bucci-Rechtweg agreed that this issue needed further discussion at the upcoming PRGLAC WG in-person meeting. Dr. Hurley agreed with Ms. Charo's comments but noted that academic institutions are extremely concerned about liability, and this concern continues a culture of exclusion. The guidance can remove things from the regulations, but that does not always mitigate an institution's underlying long-held concerns, justified or not. Dr. Pawlyk agreed that differentiating perceived liability concerns from real ones is critical. He noted that the upcoming National Academies of Sciences, Engineering, Medicine (NASEM)

report will address this issue, and he provided a link to the NASEM report. Ms. Charo said she hopes that after the NASEM report, there will no longer be a need to call for liability mitigation measures but instead a need for education about how little liability threat there really is.

Ms. Abbott proposed that the PRGLAC WG's final report not only acknowledge progress but also recommend a coordinated convener to make connections among industry, government, and stakeholders to foster relationships with industry champions, digest findings and recommendations from the NASEM report, and make progress on many of the issues raised in Recommendation 11. The WG might suggest who the appropriate convener might be. Dr. Carpenter added two links, one to the FDA's proposed rule on protection of human subjects and institutional review boards and the other to a proposed FDA rule on IRBs and cooperative research.

Ms. Tetlow asked about the development of COVID-19 therapeutics as a test case, in terms of what was learned that might help inform updates to the recommendations. Ms. Tsigas said the COVID-19 experience is an excellent example of what not to do and appears to demonstrate how much work remains to be done. Only about 2% of trials included pregnant women, according to 2020 findings. Mr. Hertz said that the advocacy community has long pushed for justification for exclusion and that its omission from the guidance is a major shortcoming. Dr. Pawlyk provided a link to the NIH Inclusion Policies webpage, which does not address pregnancy or lactation.

Dr. Kislovskiy suggested that one consideration is how the existing FDA initiatives might interact with the Centers for Disease Control and Prevention (CDC) Surveillance for Emerging Threats to Mothers and Babies around threats that particularly affect pregnant or lactating individuals. Sub-Recommendation 10C recommends that data be obtained in a timely fashion, but the definition of "timely" can differ by disease condition or threat of a novel pathogen. Dr. Kislovskiy wondered whether there are any CDC or other types of emerging threat partnerships. Dr. Reefhuis said that CDC has collaborative groups working on emerging threats during pregnancy and on birth defects and stillbirth case control studies with information on medications.

Wrap-Up and Adjournment

Dr. Carpenter made concluding comments. The NASEM report has not yet been released, but once it is, an optional briefing will be arranged. The next WG meeting will be in person on March 22, and members will be contacted about travel arrangements. Dr. Carpenter thanked the WG members for their work and dedication to this important project.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Task Force on Research Specific to Pregnant Women and Lactating Women Implementation Working Group of Council

MEETING 3 MINUTES

March 22, 2024 (Hybrid)

Task Force members present:

- **Rebecca Abbott**, Society for Maternal-Fetal Medicine
- **Susan Abdel-Rahman, Pharm.D.**, Health Data Synthesis Institute
- **Pamela Berens, M.D., FACOG**, University of Texas Health Science Center at Houston
- **Christina Bucci-Rechtweg, M.D.**, Novartis Pharmaceuticals Corporation
- **Christina Chambers, Ph.D.**, University of California, San Diego
- **Alison Cowan, M.D.**, Mirvie
- **Anthony DeLise, Ph.D.**, Novartis Pharmaceuticals Corporation
- **Camille Fabiyi, Ph.D., M.P.H.**, NICHD
- **Elena Gorodetsky, M.D., Ph.D.**, NIH
- **Julie Grimes, IBCLC, RLC**, Lactation Education Resources
- **Janet Hardy, Ph.D., M.Sc.**, Independent Consultant
- **Alison Harrill, Ph.D.**, U.S. Environmental Protection Agency
- **Kenneth (KJ) Hertz**, March of Dimes
- **Elisa A. Hurley, Ph.D.**, Consultant, Bioethics and Human Subjects Research
- **Yasaswi Kislovskiy, M.D., M.Sc.**, Drexel University College of Medicine
- **Sharon Nachman, M.D.**, State University of New York at Stony Brook
- **Sara Quinney, Pharm.D., Ph.D.**, Indiana University School of Medicine
- **Jennita Reefhuis, Ph.D.**, Centers for Disease Control and Prevention
- **Kathryn Schubert, M.P.P., CAE**, Society for Women's Health Research
- **Rachel Gandell Tetlow**, American College of Obstetricians and Gynecologists
- **Eleni Tsigas**, Preeclampsia Foundation
- **Jasmina Varagic, M.D., Ph.D., FAHA**, National Heart, Lung, and Blood Institute
- **Kaveeta Vasisht, M.D., Pharm.D.**, U.S. Food and Drug Administration
- **Kevin Watt, M.D., Ph.D.**, Spencer Fox Eccles School of Medicine, University of Utah
- **Lynn Yee, M.D., M.P.H.**, Northwestern University Feinberg School of Medicine

Opening Remarks

Emma Carpenter, Ph.D., M.S.W., Health Policy Analyst, NICHD

Dr. Carpenter welcomed the PRGLAC Implementation Working Group (PRGLAC WG) of Council members and described the meeting logistics.

Meeting Overview

Christina Bucci-Rechtweg, M.D., Novartis Pharmaceuticals Corporation, and Sue Rahman, Pharm.D., Health Data Synthesis Institute, Co-Chairs

Dr. Bucci-Rechtweg thanked the attendees for their participation and shared an overview of the progress made during the PRGLAC WG meetings of November 17, 2023, and January 19, 2024. She reminded the WG that its main objective was to evaluate the status of implementation of the recommendations outlined in the 2020 PRGLAC Implementation Plan. Specifically, the WG would review publicly available materials regarding the status of the recommendations, invite speakers from federal and nonfederal entities to discuss implementation progress and identify barriers, and submit its findings in a report to both the NICHD Council and the U.S. Congress.

So far, the WG had reviewed the status of implementation, for pregnancy and lactation, of approximately two-thirds of the recommendations. Dr. Bucci-Rechtweg explained that the first two sessions of this meeting would focus on hearing from invited speakers and conferring about the implementation status of the three remaining recommendations, which fall under Cluster B ("Education, outreach, training, and career development"):

- Recommendation 3 ("Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics")
- Recommendation 5 ("Create a public awareness campaign to engage the public and health care providers in research on pregnant women and lactating women")
- Recommendation 6 ("Develop and implement evidence-based communication strategies with health care providers on information relevant to research on pregnant women and lactating women")

Finally, the focus of the third session would be to follow up on outstanding recommendation items, to identify key themes in implementation progress, and to discuss the development of the report.

Session I: Recommendations in Cluster B (Education, Outreach, Training, and Career Development) Focusing on Training and Career Development

Presentation 1: Clinical Pharmacology Training Network

Lesly Samedy Bates, Pharm.D., Ph.D., Program Officer, Obstetrics and Pediatric Pharmacology and Therapeutics Branch, NICHD

The Clinical Pharmacology Training Network (CPTN)—formerly the Pediatric Clinical and Developmental Pharmacology Training Network—was formed in 2011 under the scope of the Best Pharmaceuticals for Children Act (BPCA) to promote career development of junior investigators and foster interdisciplinary collaboration among clinical, translational, and nonclinical investigators who study pediatric and obstetric therapeutics. Dr. Samedy Bates explained that the network was renamed in 2023 to reflect the intention to add maternal and

obstetric pharmacology to the original pediatric focus. The purpose of the program is to achieve a diverse and highly trained workforce in clinical pharmacology and therapeutics in this field. CPTN is transitioning from being co-funded to being fully funded by NICHD, and it supports training programs funded through F, T, and K mechanisms. The network's multiple components aim to provide robust and comprehensive training, mentorship, and collaboration opportunities, including interactions with other NICHD networks and the ability to connect with mentors from multiple sites across the United States. CPTN allows trainees to join the network even if their background is outside clinical pharmacology or they are not affiliated with NICHD, which further contributes to intra-network diversity.

Dr. Samedy Bates reviewed some of the network's highlights. Among other planned enhancements being implemented, CPTN has recently expanded to include K12 scholars. This K12 extension spans six sites within the network and allows scholars to come from sites that do not traditionally have clinical pharmacology research programs. CPTN also encourages networking and collaboration among trainees through its annual meeting and its active alumni network, and it has expanded its lecture series to incorporate workshops tailored for fellows.

Importantly, CPTN is developing a maternal pharmacology training program to run in parallel to its pediatric training program. By leveraging the pediatric training platform, CPTN hopes to promote maternal pharmacology and therapeutics research to address some of the gaps in appropriate medication dosing and counseling during pregnancy and lactation.

Dr. Samedy Bates said that the program's goal is to have fellows stay in the clinical research space and continue their research in pediatric and maternal clinical pharmacology. Finally, she reported that CPTN has received good feedback overall about the network and the fellowship, which reviewers say provides a solid foundation to take investigators to the next phase of their career.

Discussion With Dr. Samedy Bates

Kathryn Schubert, M.P.P., CAE, from the Society for Women's Health Research, asked whether the network has the resources it needs to expand into maternal health. Dr. Samedy Bates responded that CPTN plans to leverage its existing platform and hopes to bring in other expertise to support the maternal expansion. She added that CPTN is in the early stages of planning and would welcome feedback on how to build the maternal component. Jennita Reefhuis, Ph.D., from the Centers for Disease Control and Prevention (CDC), noted that it may be interesting for CPTN to connect with the International Society for Pharmacoepidemiology (ISPE) and potentially have CPTN fellows attend or present their work at ISPE's annual meeting.

Janet Hardy, Ph.D., an independent consultant, asked whether CPTN had a timeline for the maternal pharmacology expansion. Dr. Samedy Bates said that there is no definitive timeline. To build up a stronger maternal research network, CPTN is working on encouraging investigators to apply to the T32 program with a maternal component, but this is still in an early stage. Lynn Yee, M.D., M.P.H., from Northwestern University, noted that investigators who had been part of the Obstetric-Fetal Pharmacology Research Units (OPRU) Network would be highly motivated to apply to CPTN's maternal pharmacology training program, which could be a good starting point to find leadership.

Alison Harrill, Ph.D., from the U.S. Environmental Protection Agency, asked if, in addition to career outcomes, CPTN had looked at whether the established collaborative networks are

maintained after fellows graduate from the program. Dr. Samedy Bates responded that this had not been explicitly measured, though many of those collaborations had been observed to continue. She said that it would be interesting to quantify this, however, and that she will speak to the logistical team to explore ways to collect the necessary data.

Dr. Rahman asked for NIH's vision regarding elements of support for mentors beyond intellectual support, such as fiscal support, which has historically been low in the context of T32 programs. Dr. Samedy Bates agreed that this kind of support has been, and continues to be, low. The leadership has recognized this, and there are ongoing discussions and efforts—including work by the NICHD Extramural Training & Career Development Working Group—to address it. Dr. Samedy Bates encouraged attendees to submit a response to the Request for Information (RFI) from NICHD related to training and career development.

Presentation 2: American College of Obstetricians and Gynecologists

Rachel Gandell Tetlow, Senior Director, Government and Political Affairs, American College of Obstetricians and Gynecologists

Ms. Tetlow reviewed key ideas from the American College of Obstetricians and Gynecologists (ACOG) guidance on the inclusion of women as research participants, including the following:

- The potential for pregnancy should not mean automatic exclusion from clinical research.
- Pregnant individuals should be defined as "scientifically complex."
- Pregnant individuals should not require consent from an intimate partner to participate in research.
- There is a need to balance the risk of fetal harm with the potential for benefit and the importance of information to be gained on the health of pregnant individuals and fetuses.
- The lack of childcare and other obstacles to participation must be addressed.

These notions are also reflected in ACOG's 2024 advocacy priorities, which explicitly call for the inclusion of pregnant and lactating people in research and clinical trials. ACOG's advocacy efforts include work through the Coalition to Advance Maternal Therapeutics (CAMT), the Women First Research Coalition (WFRC), and the Friends of NICHD. ACOG also contributed to the initial draft of the Advancing Safe Medications for Moms and Babies Act and has continued to actively advocate for the next iteration of this bill.

ACOG has advocated for the inclusion of pregnant women and lactating women in research. Ms. Tetlow noted how the importance of implementing the PRGLAC recommendations was underscored recently, adding that the exclusion of pregnant individuals from the initial COVID-19 vaccine trials illustrated how barriers to this research caused harm and contributed to avoidable loss of life. Finally, Ms. Tetlow pointed out that separating the efforts under Cluster B from the implementation of the other recommendations is challenging, because those efforts would not be successful without other pieces, such as further integration of pregnant and lactating women in the clinical research agenda, removal of regulatory barriers, and liability mitigation for research in pregnant and lactating women.

Discussion With Ms. Tetlow

Dr. Bucci-Rechtweg asked to hear about the education and training component for fellows and clinical workforce and how research is being built into that core training. Ms. Tetlow said that she could not speak to the training specifically, and that ACOG works very closely with the American

Board of Obstetrics and Gynecology, the Accreditation Council for Graduate Medical Education, and the Council on Resident Education in Obstetrics and Gynecology. Looking at the future of the profession, she added, it is important to consider the challenges of the current obstetrician-gynecologist (OB-GYN) landscape, including the impact of state legislation that may restrict the comprehensive practice of obstetrics and gynecology.

Dr. Rahman asked whether ACOG's communication initiatives, beyond advocacy for legislators, were primarily directed toward ACOG members or crafted for the general public. Ms. Tetlow responded that ACOG's primary intended audience for its communications is members, though the college uses public channels as well when possible. ACOG also has a fast-growing, patient-facing website to share information about topics such as COVID-19 vaccination during pregnancy and highlighting the quality of research behind it.

Sharon Nachman, M.D., from the State University of New York at Stony Brook, noted that pediatric programs include an advocacy component as part of a 2- or 4-week elective and asked whether it was possible to connect across pediatrics and obstetrics and apply advocacy training from pediatrics to obstetrics issues. Ms. Tetlow explained that OB-GYN residency programs also include an advocacy component, adding that there may be an opportunity for connection that is likely not being taken advantage of yet. Kaveeta Vasisht, M.D., Pharm.D., from the U.S. Food and Drug Administration (FDA), asked how recent the advocacy component in residency training is and what it encompasses. Ms. Tetlow responded that advocacy has been a part of the training for approximately a decade, adding that the specific curriculum varies across institutions.

Presentation 3: Society for Maternal-Fetal Medicine

Rebecca Abbott, Senior Director of Advocacy, Society for Maternal-Fetal Medicine

The Society for Maternal-Fetal Medicine (SMFM) is a subspecialty membership organization with more than 7,000 members, many of whom are also members of ACOG. Maternal-fetal medicine specialists (MFMs) undergo 3 years of additional training to care for individuals experiencing a high-risk pregnancy. High-risk pregnancies often occur when sick women get pregnant or when pregnant women get sick: Preexisting conditions can put patients at greater risk if they get pregnant, and pregnant individuals can develop conditions that may threaten the fetus's health or their own. In both contexts, women need therapeutics during the course of their pregnancy, yet MFMs currently have to provide counseling about those therapeutics with limited data.

Ms. Abbott also outlined how PRGLAC recommendations are embedded in the work being conducted by CAMT through their five underlying priorities:

- To require FDA to remove pregnant individuals as a vulnerable research population in its regulations, which is connected to Recommendation 1 ("Include and integrate pregnant women and lactating women in the clinical research agenda")
- To establish an online hub of information on clinical trials and registries that enroll pregnant and lactating people, which is connected to Recommendations 6 and 13 ("Optimize registries for pregnancy and lactation")
- To create an education campaign, geared toward consumers and clinicians, on how to enroll pregnant and lactating people, to help these individuals and their families understand the risks and benefits of research participation, which is connected to Recommendations 5 and 6
- To initiate new clinical research at NIH on existing and new medications prescribed for pregnant and lactating people, which is connected to Recommendation 9 ("Develop

programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women")
- To secure support for the continuation of the PRGLAC WG in order to continue monitoring progress on the implementation plan, which is connected to Recommendation 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")

SMFM is also planning to develop a toolkit for clinician researchers to educate their institutional review boards (IRBs) about the inclusion of pregnant women and lactating women in research. This work, which is still in an early stage, would contribute to Recommendation 10 ("Implement a proactive approach to protocol development and study design to include pregnant women and lactating women in clinical research"), and specifically to Recommendation 10D.c ("Provide IRBs with recommended practices to facilitate inclusion of pregnant women and lactating women in study designs").

Turning to Recommendation 3, Ms. Abbott noted that the challenges and opportunities identified for obstetric and lactation pharmacology in Recommendation 3 also apply to OB-GYN clinician-scientists generally. This includes the need to enhance mentorship, to expand support for trainees and early-career investigators, and to invest in existing networks and create new ones. SMFM participates in the Friends of NICHD, the Ad Hoc Group for Medical Research, and the WFRC—efforts that help to secure funding for NIH and to increase fund allocation for OB-GYN research. Ms. Abbott also mentioned that SMFM would be interested in collaborating with NICHD and CPTN, to increase awareness of career opportunities through the society's meetings and its other interactions with fellows, as proposed under Recommendation 3A ("Develop and support training and career development opportunities in obstetric and lactation pharmacology and therapeutics for both clinical and basic science").

Regarding Recommendation 6, Ms. Abbott explained that CAMT's advocacy efforts to create an online hub and education campaign could enhance how health care providers are able to communicate with their patients about medication use and research participation during pregnancy and lactation. SMFM's work could especially advance Recommendations 6A.a ("Foster two-way communication between the research community and health care providers about obstetric and lactation therapeutic research needs"), 6A.b ("Increase health care providers' awareness of obstetric and lactation therapeutic research needs"), 6B ("Increase the engagement of health care providers to disseminate information from research findings to their patients"), and 6C.a ("Establish and maintain a readily accessible website to increase awareness of clinical research opportunities"). Ms. Abbott added that, in the future, it may be possible to incorporate some of this content into SMFM's continuing medical education (CME) modules as well.

Discussion With Ms. Abbott

Dr. Rahman asked what resources would be needed to establish the website. Ms. Abbott confirmed that the coalition had a business plan, which discussed provider and patient education, counseling tools, and the need to incorporate other institutions with expertise, including some of those present at the meeting. Ms. Abbott added that a request for $1 million for fiscal year 2025 is currently in the midst of the appropriations process. If passed, that would not be enough to complete the full project, but it would allow the process to start while more funding is sought.

However, without knowing whether that request will pass, an estimate of the expected launch date could not be provided.

Yasaswi Kislovskiy, M.D., M.Sc., from Drexel University, asked about ACOG's and SMFM's strategies to address challenges experienced by OB-GYN physician-scientists broadly, including retention in K and T programs, and what efforts are being made to understand when and why individuals leave the physician-scientist workforce. Ms. Abbott explained that most subspecialty societies are part of the WFRC, which allows them to discuss topics around women's health research and to assess training and funding mechanisms in detail. Ms. Tetlow added that there are ongoing efforts to combat burnout, but to her knowledge, no recent work had investigated when and why physician-scientists transition away from research. One reason may be that, historically, OB-GYNs have had limited protected time for research but still have to fulfill their clinical responsibilities, which could also affect their ability to secure grants later. This is anecdotal, however, and has not been explicitly studied.

Eleni Tsigas, from the Preeclampsia Foundation, asked whether professional societies are actively engaging patient advocacy groups that drive registries and advance research in their areas. Ms. Tetlow confirmed that most of the organizations mentioned throughout the session incorporate patient advocacy voices to carry out their work, with the exception of the WFRC because of its physician-centered focus.

Christina Chambers, Ph.D., from the University of California, San Diego, asked whether SMFM had studied which physicians chose not to pursue a research pathway after residency or fellowship, why they decided against it, and whether this had changed due to shifts in the legal landscape. Dr. Yee explained that OB-GYNs who finish their residency or fellowship are heavily disincentivized from choosing a physician-scientist career path. There are a number of factors that contribute to this, including limited funding and protected time for investigators who are not established researchers, challenges in securing institutional and independent K awards (K23, K08, and K01 programs) as a junior faculty member because of insufficient NICHD funding, and disincentives to conduct research because of compensation structures in the field. Dr. Yee added that capturing these factors in writing and presenting them to NICHD could help secure funding to support programs that explicitly address these issues. As funding programs shrink and Relative Value Unit compensation plans become more common, fewer individuals are choosing to undertake a physician-scientist career path.

Pamela Berens, M.D., FACOG, from the University of Texas Health Science Center at Houston, asked what organizations are doing to encourage continued research for an extended postpartum period to include lactation as a component of childbirth. Ms. Abbott agreed that the exclusion of lactation was an unresolved issue and added that SMFM would discuss potential avenues to support postpartum research that includes lactation and breastfeeding.

Dr. Vasisht asked whether SMFM had considered engaging at the community level with physicians who work with these patient communities, to educate them about opportunities for disease- or drug-based registries. Ms. Tetlow explained that registry accessibility continues to be challenging, and that efforts are ongoing to address barriers to data collection and bring registry education to ACOG members in the communities who directly interact with patients. Ms. Abbott added that SMFM shares registries and other resources through its newsletter, but more could be done to actively engage with communities.

Moderated Discussion on Cluster B: Recommendation 3

Discussion Related to Recommendation 3A

With respect to Recommendation 3A.a ("Types of training programs"), Dr. Chambers remarked that existing opportunities have not been sufficiently expanded. Dr. Yee added that the existing training and career development programs excel at preparing future independent investigators but lack the scale to support enough individuals to build the next generation of researchers in these topics. These observations point to a resourcing problem.

Sara Quinney, Pharm.D., Ph.D., from the Indiana University School of Medicine, said that Recommendation 3A.b ("Additional training opportunities") showed limited progression, highlighting the concern that senior mentors are not being replaced after they retire, which limits the ability to find mentorship for junior investigators.

With regard to Recommendation 3A.c ("Addressing challenges"), Dr. Yee reflected on the "unfortunate" loss of the OPRU Network, which could have contributed to the support of career development in therapeutics. Dr. Rahman asked about the transition between the OPRU Network and the Obstetric-Fetal Pharmacology Research Centers Program and how they differ. Aaron Pawlyk, Ph.D., chief of the Obstetric and Pediatric Pharmacology and Therapeutics Branch at NICHD, explained that the transition between those two models reflected a shift in infrastructure availability while continuing to promote obstetric and pediatric research and support junior investigator careers. He added that NICHD recently launched the Maternal and Pediatric Precision in Therapeutics Hub and reinvigorated the Maternal-Fetal Medicine Units Network and the Pediatric Trials Network in addition to CPTN. Julie Grimes, IBCLC, RLC, from Lactation Education Resources, noted that pediatricians and obstetricians are well informed about lactation, which is already included for board licensures, but there is a disconnect in other specialties when it comes to lactation education. Ms. Schubert remarked on CAMT efforts to convene other medical professional societies to discuss including this training in other specialties. Dr. Nachman added that when clinicians move to private practice, a loss of connection occurs and needs to be addressed, through training and engagement programs, to facilitate continuation of research beyond the academic context.

Focusing on Recommendation 3A.d ("Strategies to increase awareness of career opportunities"), Dr. Nachman commented on the need to emphasize office-based practice studies in pharmacology education and clinical research—and to leverage modeling and other methodologies beyond pharmacokinetics testing—to reduce time constraints for patients, allow more participants to enroll, and ensure that more primary care providers get involved in research. Ms. Tetlow added that the use of a global code for obstetric care, traditionally pulled together as a bundle payment, can hinder research. Kevin Watt, M.D., Ph.D., from the Spencer Fox Eccles School of Medicine at the University of Utah, agreed with Dr. Nachman, noting that smaller private-practice centers lack the funding and infrastructure for implementation in the community. Dr. Nachman remarked that the recent success of distal enrollment to study monkeypox illustrated the benefits of working through smaller practices. She added that IRBs should stop demanding large infrastructure and in-person consent as requirements; instead, they should encourage more flexible study designs, to reduce barriers for clinicians outside major academic institutions to pursue research careers. Dr. Kislovskiy reflected on the lack of partnerships with pharmacy and pharmacology programs. She also remarked on the irony of the lack of infrastructure to enable those of childbearing age in the workforce to pursue a physician-scientist career path, especially in the obstetrics and lactation space.

Discussion Related to Recommendation 3B

Dr. Rahman reviewed the progress updates related to Recommendation 3B ("Develop mentors in obstetric and lactation pharmacology and therapeutics for both clinical and basic science"). Though growth was limited around Recommendation 3B.a ("Increasing support for mentors"), efforts to facilitate connecting with mentors seemed to be robust, in line with Recommendation 3B.b ("Helping mentees find mentors"). With respect to Recommendation 3B.c ("Training on FDA requirements and processes"), training programs had initiatives to incorporate regulatory education.

Regarding Recommendation 3B.a, Dr. Yee asked why the NICHD portfolio did not include the K24 mechanism, citing a major deficit in mentor support, and suggested that other K mechanisms that focus on early-career researchers could include funded efforts for the mentor as well. Dr. Pawlyk again encouraged attendees to submit recommendations through the NICHD training and career development RFI.

Dr. Rahman noted that there should be obstetric and lactation funding from other institutes besides NICHD. Dr. Pawlyk cited efforts through the NIH Pediatric Research Consortium to engage other institutes and centers in a more formal capacity in order to discuss training and career development, encourage investigators to apply for K and T grants across institutes, and leverage the opportunities provided under the BPCA legislation.

Discussion Related to Recommendation 3C

Dr. Rahman said there has been limited progress on Recommendation 3C ("Increase the knowledge and engagement of health care providers regarding obstetric and lactation pharmacology and therapeutics"), and WG members generally agreed with that assessment. Ms. Tsigas added that pharmacology education did not seem to reach OB-GYN generalists in the community.

Session II: Recommendations in Cluster B (Education, Outreach, Training, and Career Development) Focusing on Education and Outreach

Presentation 1: CDC's Communications Efforts Related to Medications and Pregnancy

Kara Polen, M.P.H., Associate Director for Communications, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

In the past, formative research has indicated that pregnant individuals receive conflicting information about continuing medications. As a result, they are often reluctant to use medication because of uncertainty. Surveys found that the primary concern for women was short- and long-term harm to the fetus, followed by concerns about their own health and well-being. Though OB-GYNs were the main trusted source of information during pregnancy, patients also relied on recommendations from friends and relatives, as well as online blogs and social media. Participants reported feeling more confident in their decision to use medication if messages from clinicians were consistent across providers and validated by personal stories and other sources they trusted. The findings from prescriber and pharmacist surveys led to improved digital resources to engage with patients. This included developing new educational materials, updating pregnancy and maternity web content, and collaborating with bloggers and influencers to improve dissemination.

Ms. Polen reviewed some of CDC's ongoing research efforts regarding communications. In recent surveys, patients have reported interest in receiving information from their providers through a variety of channels, including links to online resources after appointments, videos, text messages, and printed handouts. CDC is also assessing risk communication through its birth defects case control study (BD-STEPS), which includes an analysis of patient discussions with health care providers about treatment options during pregnancy. Another ongoing project focuses on perceptions of risk during pregnancy. This work, which is being conducted through a cooperative agreement with Karna, will study several pregnancy-related focus groups to assess risk perception and test communication strategies within multiple scenarios.

Regarding information dissemination, Ms. Polen outlined some of CDC's initiatives to deliver clear messaging and translate new research findings into actionable content for general audiences. Examples included sharing short videos on social media to combat misinformation, posting patient testimonials that would include in the caption key information, and providing links to additional resources.

CDC partners with MotherToBaby, which provides insight into common concerns among its audience and helps disseminate updated information more broadly. CDC also works with clinical organizations, such as ACOG and SMFM, to ensure consistent recommendations, advance health provider education, and engage trusted messengers.

Within the next year, CDC will work on assessing information available in provider-facing digital platforms and in pregnancy platforms to point out resource gaps. Another effort will be to extend CDC partnerships with nurses, midwives, and nurse practitioners. Formative research findings have also identified long-term opportunities to improve training for pharmacists and physicians across other specialties, enhance patient-facing materials through personal stories and engaging visuals, collaborate with experts in lactation and other areas, and create a consolidated hub to house information on this topic.

Discussion with Ms. Polen

Camille Fabiyi, Ph.D., M.P.H., from NICHD, asked about the opportunity to promote the inclusion of pregnant and lactating women in research through those CDC efforts. Ms. Polen said that the current CDC website already links to a number of resources, which could be expanded.

Ms. Tetlow asked about the expected outcome of the focus groups. Ms. Polen explained that the ongoing focus group work—which is not specific to medications and pregnancy—seeks to inform communication efforts across the division. The end product would be a set of high-level findings to promote more effective communications across all topics.

Presentation 2: MotherToBaby

Christina Chambers, Ph.D., M.P.H., Distinguished Professor, Department of Pediatrics, University of California, San Diego

MotherToBaby is an initiative that provides current, evidence-based information on the risks and benefits of medications and other exposures during pregnancy and lactation. Right now, there are 14 services, which serve all U.S. states and territories through a national routing system. Depending on the service, funding sources include state and local resources. The Health Resources and Services Administration (HRSA) and CDC provide network-wide funding. The network receives approximately 40,000 queries annually, predominantly from pregnant and

lactating individuals. MotherToBaby has also collaborated with CDC on multiple occasions to provide urgent public health information on pregnancy and breastfeeding during critical events, including Hurricane Katrina, Zika infection, and COVID-19 infection and vaccinations.

Dr. Chambers reviewed the range of methods in which MotherToBaby communicates directly with consumers. More than 300 MotherToBaby fact sheets exist on a variety of exposures during pregnancy and breastfeeding. Fact sheets, which are available in English and Spanish, are updated annually and can be accessed and downloaded for free through the website and the National Library of Medicine (NLM) portal. Since its launch in 2017, the MotherToBaby podcast has covered in detail many topics in its 67 episodes, which often include interviews with leaders and experts in the field. The MotherToBaby blog, which provides practical information, is published monthly in English and Spanish. Regarding lactation, LactRx by MotherToBaby is a free mobile app to access LactMed, an information resource supported by NICHD and NLM and focused on safety of medications, plus other exposures during lactation.

MotherToBaby collaborates with clinicians as well. One example of this is HRSA's National Maternal Mental Health Hotline, which can warm-transfer callers to MotherToBaby for information on medications or other exposures during pregnancy and lactation. MotherToBaby also collaborates with ACOG, CDC, and SMFM to co-sponsor quarterly educational webinars for clinicians; SMFM, meanwhile, distributes MotherToBaby fact sheets through the society's newsletter. In addition, MotherToBaby hosts a Human Teratogens live virtual course, which is offered in alternating years.

Dr. Chambers also discussed MotherToBaby Pregnancy Studies, a research program to assess the impact of medications, vaccines, and health conditions on pregnancy and infant outcomes. The program enrolls participants across the United States and Canada through a single research center. It captures information from telephone interviews, medical records, and a specialized dysmorphological examination for live-born infants. The information services refer individuals who may be interested and eligible to the studies. The results of the studies feed back into the information made available through MotherToBaby. This is paired with a human milk biorepository that is capturing samples and data about exposures during lactation.

Discussion With Dr. Chambers

Ms. Schubert asked whether MotherToBaby engaged nurse practitioners and other health care providers in addition to physicians. Dr. Chambers cited previous partnerships with Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), and the American College of Nurse-Midwives (ACNM) as part of an extensive program to engage with various types of providers in the obstetrics and lactation space. Ms. Polen added that CDC also collaborates with ACNM and AWHONN on alcohol and pregnancy work and is now looking to expand its engagement portfolio with these groups.

Ms. Tetlow asked about engaging pharmacy organizations, referencing reports of pharmacists who refuse to vaccinate pregnant people or who administer the incorrect vaccine. Dr. Chambers agreed that pharmacists often do not receive this key training. She said that MotherToBaby provides some of that education through presentations at major pharmacy meetings. Ms. Polen noted that other divisions under CDC closely collaborate with pharmacy groups, although hers does not.

Ms. Grimes asked what outreach to lactation professionals had taken place. Dr. Chambers mentioned working with the Academy of Breastfeeding Medicine to disseminate information about LactRx. She said that more can be done to ensure that lactation consultants know where they can find this information.

Moderated Discussion on Cluster B: Recommendations 5 and 6

Discussion of Recommendation 5

Ms. Abbott asked what the public awareness campaign described in Recommendation 5 might look like and what may be missing. Dr. Chambers reflected on the lack of public awareness indicated by the volume of queries reaching MotherToBaby. She remarked on the need for an improved public awareness campaign to state that this information is available and explain how to access it. Ms. Tsigas asked what other entities beyond MotherToBaby are doing in this space. Dr. Chambers mentioned that CDC, Text4baby, past NICHD efforts, and some commercial initiatives did some work in this space, though none in the scale of MotherToBaby. Dr. Reefhuis echoed that there is an absence of other organizations doing comparable work.

Dr. Bucci-Rechtweg asked the WG to identify potential challenges in bringing all the stakeholders to the table. Dr. Reefhuis remarked on the lack of connectivity among different providers—for example, between a specialist treating a patient's disease and the patient's OB-GYN, as well as the pharmacist who will ultimately provide the medication. Dr. Chambers added that most specialists tend to refer their pregnant patients to OB-GYN care as soon as they find out about the pregnancy; identifying the few specialists interested in reproductive health in their field is necessary to drive initiatives forward. She also pointed out an important gap between obstetric care and pediatric care, arguing that obstetricians should discuss lactation before childbirth and remarking on the disconnect between the child's and the adult's electronic health records (EHRs) during lactation. Adult medication results are recorded in one EHR, while the effects on the child are recorded separately in the other EHR. Dr. Hardy added that disease-based registries are typically run by specialists who communicate very little with OB-GYNs.

Ms. Tetlow said that the switch from lettering to explanatory statements brought by the new Pregnancy and Lactation Labelling Rule (PLLR) is seemingly positive, yet also resulted in concerns from ACOG members over clarity and conciseness during conversations with patients.

Regarding Recommendation 5A ("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"), Dr. Bucci-Rechtweg asked the WG to consider whether current communication strategies adequately address the risk of both taking and not taking medication. Relatedly, Dr. Hurley asked about when someone contacts MotherToBaby, wondering how much of the conversation is meant to help assess relative risks. Dr. Chambers explained that it was equally weighted, and that although the PLLR legislation now requires this information to be included in the label, there is concern that health care providers and patients may not read the whole label and may miss this information. Kenneth (KJ) Hertz, from March of Dimes, asked how many of the people who contact MotherToBaby have already discussed the risk of taking or not a medication with their health care provider. Dr. Chambers said that both scenarios are common, though this has not been formally quantified. She noted that MotherToBaby staff always encourage callers to discuss the information they received from MotherToBaby with their providers.

Dr. Nachman asked whether there is a list of medications that are lacking in terms of the content in their package insert and suggested explicitly allocating funding to write and disseminate guidelines for these drugs. Dr. Fabiyi referred to a discussion at the January 2024 PRGLAC WG meeting about NICHD publishing an RFI in 2023 that requested nominations for drugs, vaccines, and dietary supplements that should be prioritized for research, with plans to collect feedback from stakeholders in a meeting later in the summer of 2024. Dr. Chambers added that the two chief sources of information regarding use of over-the-counter medications are BD-STEPS and the MotherToBaby pregnancy registries, which provide most of the information for fact sheets.

Dr. Bucci-Rechtweg summarized the state of implementation for Recommendation 5 as ongoing, with more progress needed in two areas:

- Focusing some public awareness on the risks of not taking medications during pregnancy and lactation, as well as helping all stakeholders understand why this is a critical component of the discussion
- Exploring other opportunities to expand these conversations into the lactation expert community and strengthen the connectivity between different stakeholder groups

Dr. Reefhuis remarked on the need to continue to educate the public about what *risk* and *prevalence* mean. Dr. Rahman added that the upcoming results from the CDC research on risk perception and communication should provide some guidance to inform those discussions.

Ms. Grimes pointed out that there had been no discussion of the risks of not breastfeeding and that there had been little progress on this front. She said that, because of pushback against education efforts for health care workers, talking about the risks of not breastfeeding incurs guilt, so the topic is often avoided. She added that this needs to be addressed before downstream problems can be tackled.

Dr. Hurley commented on the importance of making the connection for the public between the information about risks that is known or not and the need for more research to fill those gaps, including how one can get involved in that research. Dr. Rahman wondered whether CDC risk communication studies would ask whether respondents who said that they did not have enough information would be willing to participate in research. Ms. Polen explained that opportunities to participate in research are outlined on the website, but CDC will look into incorporating these questions into the surveys.

Regarding both Recommendations 5 and 6, Dr. Kislovskiy suggested defining risk as a patient-centered outcome for future research and incorporating the advances seen in the family planning research space into obstetrics and lactation pharmacology. Ms. Tetlow underscored that more research is needed, despite ongoing efforts that deserve to be acknowledged. Dr. Bucci-Rechtweg agreed, remarking on the recurring theme of underfunding. Ms. Schubert added that there needs to be a dedicated funding stream for these initiatives and underscored the need—both in terms of public awareness and provider education campaigns—to have clear calls to action for intended audiences. This also speaks to the interconnectivity among health care provider training, research efforts, and public awareness campaigns. Dr. Bucci-Rechtweg concurred, adding that these recommendations are highly interconnected and cannot advance independently, because they rely on the others' progress.

Dr. Reefhuis noted that the childrearing population is replaced every few years. This means that communication campaigns are constantly directed at a new group of women, based on age as

well as other factors that include evolving demographics and information sources that the population relies on. Dr. Bucci-Rechtweg added that prioritizing where messages most resonate—friends and family potentially have an outsized impact—can also depend on cultural differences.

Discussion of Recommendation 6

Ms. Tsigas reflected on the public's lack of distinction between the effects of a medication being uncertain and the effects being known to cause problems during pregnancy or lactation. There is a general belief that pregnant individuals should not be taking any medications—and that health care providers recommend not taking them—because medications are known to be harmful, as opposed to their risk being unclear. This is related to communication around research participation for drug development to address pregnancy complications, which could be hindered given this pervasive notion that taking medications during pregnancy is inherently bad. Dr. Bucci-Rechtweg said that highlighting why this research is necessary and how it will inform risk and benefit discussions is an important component of Recommendation 6A ("Increase the knowledge of health care providers regarding obstetric and lactation therapeutics and research needs") that should involve not only OB-GYNs but also other specialties.

Dr. Yee remarked on a lack of partnerships with those who develop, test, and implement evidence-based communication strategies, and proposed that funding be allocated to foster those collaborations. Dr. Kislovskiy added that involving behavioral science experts early on in the design of communication strategies would also be valuable. Dr. Berens noted that lactation therapeutics include not only medications taken during lactation but also drugs taken specifically to address lactation, which are often overlooked.

Ms. Schubert asked about opportunities related to FDA's patient-focused drug development meetings. Dr. Vasisht said that FDA led workshops on topics relevant to pregnancy and lactation that include webinars for health care providers on the PLLR and on opportunities to engage in research for their pregnant and lactating patients.

Dr. Bucci-Rechtweg asked the WG to consider the implementation status of Recommendations 6C ("Increase the engagement of health care providers to discuss participation in clinical trials, research, and registries") and 6D ("Develop appropriate strategies for sharing and interpreting research findings and risk"). Dr. Yee said that one challenge regarding health care providers who do not conduct research is that compensation structures in both academic and private practice settings reward clinicians for high volume patient care, but do not incentivize or allow time for enrolling patients in registries or clinical trials. She also suggested monitoring the outcomes of the antiretroviral pregnancy registry's pilot program, which pays clinicians to upload data—a way to engage those who might not otherwise be inclined to contribute data. Dr. Chambers added that another return of value for clinicians may be information to help treat their patients.

Session III: Follow-Up on Past Items, Moderated Discussion, and Report Development

Follow-Up on Past Items

Dr. Bucci-Rechtweg said that the update from the Office of Human Research Protections (OHRP) at the U.S. Department of Health and Human Services (HHS) received the day of the

meeting would allow the PRGLAC WG to discuss the following pending items within Recommendations 1, 4 ("Remove regulatory barriers to research in pregnant women"), and 10:

- Recommendation 1C: "HHS should develop guidance to facilitate the conduct of research in pregnant women and lactating women"
- Recommendation 4A: "Modify subpart B of the Common Rule:
    - "Change 46.204(e) in subpart B to maternal consent alone
    - "Add in the option of 'Minor increase over minimal risk' from subpart D to 36.046"
- Recommendation 10A: "Investigators/sponsors must specifically justify exclusion in study design"

Ms. Schubert said that the OHRP update confirmed that these recommendations required additional progress. Ms. Tetlow remarked on the lack of discussion reported in the OHRP update on changes to the requirement for consent. The WG also pondered whether the recommendations needed to be directed higher up within HHS, based on the OHRP update, and wondered about potential differences depending on the administration and the likelihood of encountering political appointees as opposed to career staff if escalating within the HHS hierarchy. Ms. Abbott suggested focusing more on the guidance components, which OHRP has more power over, as opposed to the regulatory components. WG members agreed with Ms. Abbott's suggestion.

Dr. Pawlyk noted that although NIH inclusion governance policies require NIH clinical trials to report the age of all participants, to ensure lifespan inclusion, report requirements for the inclusion of pregnant women and lactating women do not exist. That means that the recruitment of these two populations in NIH trials is not tracked. Ms. Schubert agreed that this is important and said that progress on this is needed soon. Dr. Nachman added that it was possible to estimate the number of pregnant and lactating individuals enrolled in trials through some of the networks represented in the PRGLAC WG.

Overall, the WG agreed that there was not enough progress in these components; further attention—and perhaps an escalation, given how much time has passed since the initial recommendations were put forward in the 2018 PRGLAC Report—is therefore required. Guidance may move faster than policy and provide experiential data to refine regulation.

Dr. Bucci-Rechtweg asked the WG to discuss the call for congressional action that members had previously deemed necessary for Recommendations 8 ("Develop separate programs to study therapeutic products used off patent in pregnant women and lactating women using the NIH BPCA as a model") and 9, specifically regarding the following components:

- Recommendation 8A: "Provide specific funding"
- Recommendation 9B: "Consider a Biomedical Advanced Research and Development Authority (BARDA)-like model and the NIH vaccine model that takes clinical development up to phase II"

Regarding Recommendation 8A, Ms. Schubert said that more funding needed to be explicitly allocated to pregnancy and lactation research, independent of BPCA and the Pediatric Research Equity Act. Dr. Watt noted that lobbying efforts in pediatrics have been successful, and Ms. Tetlow added that the groundwork has been laid to authorize and support a call for this specific funding. Ms. Abbott emphasized that this should not fall exclusively on NICHD, but on other institutes and funding agencies as well.

Regarding Recommendation 9B, Dr. Harrill suggested that greater nonclinical exploration—including *in vitro* and computational tools and the study of basic metabolism to understand medication transfer through the placenta and the mammary glands—is needed to reduce the risks inherent in clinical trials. Anthony DeLise, Ph.D., from Novartis Pharmaceuticals Corporation, agreed, citing the success of previous incentive structures to bring in industry partners and adding that this is a good opportunity to push part of that work back to the pharmaceutical industry before approval, rather than exclusively through postapproval studies. Dr. Bucci-Rechtweg proposed revising the wording in Recommendation 9B to replace the term *consider* with stronger language, plus adding a new subpart to Recommendation 9 to capture nonclinical research promotion. The WG was in agreement.

Moderated Discussion of Open Items From Cluster B

Dr. Rahman asked the WG to consider any outstanding items concerning Recommendation 3, 5, or 6.

One member said that, regarding Recommendation 6A.c ("Encourage health care providers' engagement by increasing continuing education opportunities"), more progress is needed in medical school and CME modules, and that parties beyond OB-GYNs—including psychiatrists and other specialists—should be brought into the conversation. Dr. Rahman asked the group to consider who should take charge of this recommendation. Group members responded that professional organizations for each specialty should incorporate these topics into their certification requirements, perhaps in collaboration with certifying.

Regarding Recommendation 5B ("Engage stakeholders such as HHS, professional societies, industry, advocacy groups, and public and global partners"), Dr. Harrill noted that there had been little discussion of global partners. Dr. Chambers cited a partnership between MotherToBaby and the equivalent European network of information services. Ms. Polen referenced CDC's collaborations with the World Health Organization and other international bodies on efforts such as those combating Zika and COVID-19, though there were challenges because of inconsistency between global and U.S. recommendations. Dr. Nachman mentioned meetings with global partners to collaborate on HIV efforts and shared a tuberculosis and pregnancy report published in February 2024. Dr. Hardy noted that there is an added difficulty with this communication collaboration in the postapproval stage, as opposed to preapproval, because of differences in labeling standards and rules. Ms. Tsigas remarked on the need for global partnerships in prioritizing clinical research and drug discovery as it relates to pregnant and lactating individuals. Dr. Bucci-Rechtweg clarified that the global standpoint on this particular recommendation made sense, because the U.S. Congress can more easily engage in those global partnerships around communication efforts, as opposed to other areas where international collaborations are difficult because of specific funding allocations from U.S. sources.

Report Development

Dr. Carpenter reviewed the scope of the report, reminding the WG that it is charged with assessing the progress of recommendation implementation, rather than making any new recommendations. She also explained that major disagreements or lack of consensus would be noted similarly to how they appeared in the original 2018 PRGLAC Report.

Dr. Bucci-Rechtweg shared the outline of the report, divided into four sections:

1. The *Introduction* section will contain an overview of the original PRGLAC Report, the WG, and the information-gathering activities.
2. The *Implementation Updates* section will feature one subsection per recommendation, including a comprehensive characterization of implementation status and specific considerations for each recommendation.
3. The *Themes* section will discuss overarching themes regarding barriers or actions that impact all the recommendations or the pregnancy and lactation research space.
4. The *Conclusion* section will summarize the findings of the PRGLAC WG.

Dr. Carpenter next reviewed the timeline for the report, highlighting that the WG would have the chance to review a draft from May 13 to May 24. The final Council presentation, which is open to the public, will take place on June 3, 2024. Dr. Kislovskiy asked whether there would be an opportunity for the WG to meet after the submission of the report, and Mr. Hertz asked whether it would be disseminated to the public. Laura Berkson, J.D., from the Office of Legislation, Public Policy, and Ethics at NICHD, said that the report will not be open for public comment, but it will be shared online and through other channels if the WG considers this appropriate. Ms. Abbott added that CAMT would be able to assist in this effort. Dr. Hardy said that this is a progress report, and that more evaluations will be required in the future.

Dr. Bucci-Rechtweg reviewed the overarching themes that arose from the WG's discussions:

- Additional assessment of implementation progress is needed in order for this work to continue beyond the report.
- The report should distinguish the differences in challenges and implementation plans for pregnancy and lactation.
- Ownership of recommendations may be disparate or unclear.
- The report should outline that multiple stakeholders, public and private, should be engaged in these recommendations.
- Some recommendations require additional resources or congressional action.

Dr. Bucci-Rechtweg and Dr. Rahman invited the WG members to share their views about these overarching themes in sequence.

Dr. Yee agreed with the overarching themes, emphasizing the need for additional resources and congressional action in order to make implementation possible. She also remarked that pregnancy and lactation, though separate, should be addressed cohesively and not in conflict with each other.

Dr. Vasisht noted that the demarcation between lactation and pregnancy was due to an initial concern that lactation had been overlooked. She added that the limitations of the report should be outlined, acknowledging the need for multiple stakeholders for implementation and the lack of representation of industry voices in the PRGLAC WG.

Jasmina Varagic, M.D., Ph.D., FAHA, from the National Heart, Lung, and Blood Institute (NHLBI), agreed that the themes were appropriate, including the separation between lactation and pregnancy, and emphasized the need for additional funding.

Ms. Tsigas agreed with the themes and the demarcation between lactation and pregnancy as two distinct populations that have been historically underrepresented, with unique challenges that require different approaches and resources. She also remarked on the need for responsibility

and accountability when it comes to recommendations, which is difficult if ownership is kept vague. She added that COVID-19 illustrated how lacking inclusion of pregnant and lactating individuals had been in research, which could be an important detail to include in the *Introduction* section.

Ms. Schubert agreed that there is a need to illustrate why the work outlined in the report is still important, and why the separation between lactation and pregnancy exists. Regarding the multiple stakeholders, she suggested calling on specific groups, rather than single entities, to take ownership of recommendations, plus listing organizations or types of organizations that can facilitate implementation.

Dr. Reefhuis remarked that equity, though mentioned under the initial ethical considerations, was not explicitly built into the recommendations, but has been increasingly showcased. She also commented on the need to keep the scientific and funding discussions separate.

Dr. Quinney emphasized the need for funding to support directives that bring together multiple stakeholders, in addition to other mandates. She also commented on the lack of a defined measure of success for many of the recommendations, which are seeing incremental progress but do not have a defined goal. Furthermore, she agreed that the term *consider* is not conducive to determine whether a recommendation has been fulfilled.

Dr. Kislovskiy agreed with the overarching themes and underscored the gap between incorporating stakeholders—including pharmacy and industry partners, behavioral scientists, professional societies, and community voices—and securing sufficient resources. She also supported the idea of the PRGLAC WG as a place to convene multiple stakeholders and a venue where a check-in process can be established.

Dr. Hurley said that the themes were appropriate, agreeing on the separation between pregnancy and lactation and on the concerns over lack of clear ownership potentially leading to inaction. She suggested that the PRGLAC WG work to bring stakeholders to the table. She also pondered the need to gather information about results after full implementation, such as whether encouraging health care providers to speak to their patients about clinical research led to more pregnant and lactating individuals getting involved in that research. She said it would be important to acknowledge the magnitude and expected timeline of these goals in the report when discussing progress toward achieving said goals.

Mr. Hertz agreed with the overarching goals, adding that assigning ownership to the recommendations, to the extent possible, would be helpful. He also supported the idea of differentiating short- and long-term goals.

Regarding multiple stakeholders, Dr. Watt said that almost every institute beyond NICHD has some stake in pregnancy and lactation, and that this should be explored for future partnerships.

Dr. Nachman asked how the report would outline approaches and resources for academic and nonacademic centers separately.

Dr. Harrill remarked on the need to assess recommendations within the scope of basic, translational, and clinical research. She also underscored that not all recommendations have shown progress, which is important to make clear when using the term *progress report*.

Dr. Berens agreed with the overarching themes and the points raised so far, including the separation of pregnancy and lactation.

Dr. Hardy cited phrasing from the original report that should be included in the new report, adding that pregnant and lactating persons should not be protected from participating in research but rather should be protected through research. She also remarked on the existence of less evidence available for lactation and safety compared to pregnancy and underscored the need to keep lactation separate from pregnancy in order to ensure sufficient evidence exists for each one. Regarding ownership of recommendations, she said that suggesting stakeholders would be useful.

Ms. Grimes agreed that unclear ownership has resulted in reduced progress, and that identifying multiple stakeholders would help to speed up implementation.

Elena Gorodetsky, M.D., Ph.D., from NIH, said that federal bodies can offer guidance to help stakeholders work together, thereby encouraging collaboration across institutes and an information exchange with other partners whose efforts may be unknown to the PRGLAC WG.

Ms. Tetlow agreed with the themes and remarked on the differences between 2018—when the original PRGLAC Report was published—and the present, noting that it is now well established that maternal mortality is an important concern. She also commented on the perception of liability as something to keep in mind and to challenge when working with the private sector.

Dr. Fabiyi agreed with the overarching themes and commented on the importance of partnerships in advancing recommendations among multiple stakeholders.

Dr. DeLise agreed with the themes. He added that additional resources should include not only funding but also industry partners that could help fill in gaps in basic science and clinical research.

Alison Cowan, M.D., from Mirvie, acknowledged the increasing recognition of maternal mortality and improvement in quantification, but also remarked on pending items to address, such as racial inequalities. Additionally, she emphasized that objective metrics should be referred to as a key priority whenever possible.

Dr. Chambers agreed that it is possible to track where pregnancy is excluded, but not where it is included. She said that even if lactation and pregnancy are separated, this demarcation should not imply losing track of synergies between both populations. She added that assigning ownership of a process recommendation to multiple stakeholders could lead to improved implementation.

Ms. Abbott agreed with the overarching themes and suggested that the report distinguish between what requires congressional action and what can be done without explicit new authorization. She also agreed that there is a need to expand funding sources beyond NICHD and NIH.

Following discussion from WG members, Dr. Rahman opened the floor to other attendees. Dr. Pawlyk remarked on the need to study postpartum conditions that require treatment as part of the PRGLAC WG scope regardless of lactation and transfer through breastfeeding. Alison Cernich, Ph.D., Deputy Director of NICHD, thanked everyone present and added that NICHD tends to lead on these issues because it has the largest maternal health portfolio and is the

largest funder of lactation research. But it also partners with NHLBI and other institutes and continues to advocate within NICHD and build relationships to ensure that these issues are at the fore.

Ms. Tsigas said that including a statement for lay audiences is important so that people can understand whether the fetus is at risk. It also has to be clear, she added, that science has advanced to the point that this research can be performed safely. Dr. Reefhuis added that when concerns over a certain medication are mentioned, a discussion of what the alternatives are should follow. Dr. Yee commented on the concern of women participating in research "as a vessel" only for the sake of the fetus. Separating pregnancy and lactation considerations should not give the appearance that lactation research is important only for the child; there is a need to underscore the value of this research for the health of the person who is lactating.

Dr. Carpenter said that the new report will contain the text of the original recommendations along with a progress update and the nuance and caveats for each, including the general consensus of the PRGLAC WG and any major dissents.

Concluding Remarks and Adjournment

Dr. Bucci-Rechtweg thanked Dr. Carpenter and the other organizers of the meeting, as well as the speakers. She also acknowledged the difficulty of assessing implementation progress and thanked the PRGLAC WG members for sharing their insights.

Dr. Carpenter then reviewed travel logistics, thanked all in attendance for their work and dedication to this important project, and adjourned the meeting.

Appendix IV: List of Acronyms

ACOG	American College of Obstetricians and Gynecologists
AI	Artificial intelligence
APR	Antiretroviral Pregnancy Registry
ARIA	Active Risk Identification and Analysis
BC	Biomarkers Consortium
BD-STEPS	Birth Defects Study To Evaluate Pregnancy exposureS
BPCA	Best Pharmaceuticals for Children Act
CAMT	Coalition to Advance Maternal Therapeutics
CDC	Centers for Disease Control and Prevention
CDEs	Common data elements
CFR	Code of Federal Regulations
CME	continuing medical education
Complement-ARIE	Complement Animal Research In Experimentation
ConcePTION	Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology, and Breastfeeding to Improve Outcomes Now
CPTN	Clinical Pharmacology Training Network
DASH	Data and Specimens Hub
EHR	Electronic health record
FDA	U.S. Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
HHS	U.S. Health and Human Services
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMI	Innovative Medicines Initiative
IND	Investigational new drug application

IRB	Institutional review board
MFMU	Maternal–Fetal Medicine Units
MPRINT	Maternal and Pediatric Precision in Therapeutics
NACHHD	National Advisory Child Health and Human Development
NASEM	National Academies of Sciences, Engineering, and Medicine
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NOFO	Notice(s) of Funding Opportunity
NRN	Neonatal Research Network
OB-GYN	Obstetrician-gynecologist
OHRP	Office for Human Research Protections
ONC	Office of the National Coordinator for Health Information Technology
PD	Pharmacodynamic
PK	Pharmacokinetic
PLLR	Pregnancy and Lactation Labeling Rule
PREA	Pediatric Research Equity Act
PTN	Pediatric Trials Network
RFI	Request for Information
PRGLAC	Task Force on Research Specific to Pregnant Women and Lactating Women
RWD	Real-world data
RWE	Real-world evidence
SACHRP	Secretary's Advisory Committee on Human Research Protections
SCDM	Sentinel Common Data Model
SMFM	Society for Maternal–Fetal Medicine
VICP	Vaccine Injury Compensation Program