

**TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT  
WOMEN AND LACTATING WOMEN**

**Report Implementation Plan**

**To the Secretary, Health and Human Services**

**August 2020**

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## Overview: Themes and Issues

### *Introduction*

As the 2018 Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) Report to the Department of Health and Human Services (HHS) Secretary documents<sup>1</sup>, longstanding obstacles to inclusion of pregnant women and lactating women in clinical research studies have limited the collection of data to support the safety and appropriate dosing of medications and other therapeutics used during pregnancy and lactation. Following submission of the 2018 PRGLAC Report, the Secretary extended PRGLAC's charter, asking for further guidance on implementation of the 15 Recommendations included in the Report. While some steps have been taken to address obstacles to this research, such as the recent change to the federal regulations protecting human subjects who participate in research<sup>2</sup> (the "Common Rule"), the culture of protecting pregnant women and lactating women from research has proven resistant to change. The presumption that ceasing use of medications throughout pregnancy and lactation is "healthier" for a woman and her offspring is inaccurate in many cases and may actually endanger their health. This danger applies not only to treatments for conditions arising directly from pregnancy, but even more so for treatment of conditions that occur in reproductive-aged women, whether pregnant, lactating, or neither. In the vast majority of cases, the scientific evidence does not support either continued use or cessation of using the therapeutics, primarily because that evidence does not exist or is insufficient. Inclusion of pregnant women and lactating women in vaccine and treatment trials during the current SARS-CoV-2 pandemic illustrates this point.

### *PRGLAC Implementation Plan: Common Themes*

Just as the recommendations made by the PRGLAC in its 2018 report comprised an interrelated response to congressional concerns about inclusion of pregnant and lactating women in clinical research studies, the implementation steps developed for each of the recommendations are also integrated throughout the plan. In framing these potential steps, several common themes emerged, providing a useful overview of the major steps needed to move ahead.

#### **Leveraging or expanding existing federal programs or networks**

Most of the working groups discussed which existing federal programs, or components of those programs, could serve as potential models for efforts to maximize inclusion of pregnant women and lactating women in clinical research studies. The groups also recognized that existing research networks supported by the federal government could be expanded to further research on therapeutics used during pregnancy and lactation (Recommendations 1, 2, 3, 7, 8, 9, 11, and 12).

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<sup>1</sup> <https://www.nichd.nih.gov/about/advisory/PRGLAC>

<sup>2</sup> <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html>

## **Developing a systematic plan to collect data in pregnant women and lactating women**

A systematic plan for the timely collection of data (e.g., safety, pharmacokinetic [PK], pharmacodynamic [PD]) during pregnancy and lactation must be established (Recommendations 1, 2, 10, and 13).

## **Developing research tools and strategies**

Addressing practical considerations that have posed difficulties for researchers or would expand the power of their studies by allowing comparisons or linkages of study cohorts, could facilitate more research on therapeutics used during pregnancy and lactation. Use of a central Institutional Review Board (IRB) for multisite studies, agreement on common data elements across studies, and the development of preclinical models offer some examples (Recommendations 1, 2, 7, 10, 12, and 13).

## **Considering trial design**

For ethical and other reasons, the gold standard randomized clinical trial design to test therapeutics used during pregnancy and lactation may not be feasible. Several of the implementation steps suggest exploring alternative trial designs that would more easily accommodate inclusion of a diverse group of pregnant women and lactating women in study populations (Recommendations 2, 6, and 10).

## **Utilizing registries and usable data sources**

Datasets that can be linked (e.g., pregnant women, infants) would help researchers compare results across studies. Encouraging women to participate in existing clinical, industry, or research registries would facilitate the creation of research hypotheses and clinical trial recruitment (Recommendations 2, 6, 7, 8, 11, 12, and 13).

## **Establishing a prioritization process for studying therapeutics used during pregnancy and lactation**

Over 90 percent of women use at least one medication during pregnancy, and about 70 percent use at least one prescription medication.<sup>3</sup> According to one recent source, 90 to 99% of women receive at least one medication during the first week after delivery.<sup>4</sup> Many women who become pregnant or are lactating already have chronic conditions needing treatment, in addition to conditions that may arise as a result of pregnancy. Consequently, because so few studies have been conducted, some prioritization is necessary to determine which therapeutics should be studied first, possibly based on current processes established for other areas of research (Recommendations 2, 8, and 9).

## **Addressing ethical considerations, liability concerns, and potential incentives**

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<sup>3</sup> <https://www.cdc.gov/pregnancy/features/pregnancy-meds-keyfindings.html>

<sup>4</sup> Wambach, K., and Spencer, B. (eds.), 2021, *Breastfeeding and Human Lactation*, 6<sup>th</sup> Edition, Jones and Bartlett Learning, Burlington, MA, p. 127.

Although revisions to the federal regulations for protection of human subjects (the “Common Rule”) participating in research removed pregnant women as an example of a “vulnerable population,” ethical concerns and the potential for liability remain for research conducted during pregnancy and lactation. While no single solution to these concerns may be apparent, a mix of incentives and continued protections (informed consent) may partly address these issues (Recommendations 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10).

### **Fostering education and awareness**

Building awareness of the changes to the federal regulations and encouraging diverse groups of women to participate in research will require making pregnant and lactating women, and the healthcare providers who care for them, aware of the options for participating in clinical research (Recommendations 3, 5, 6, and 10).

### **Creating partnerships**

Creating a culture change that allows for research on therapeutics used during pregnancy and lactation could be greatly bolstered through collaborations and partnerships among the many stakeholders on this issue, including partnering on the design of research, sharing of data and/or biospecimens, clinical trial recruitment, and funding. Some existing collaborations have great potential for expansion (Recommendations 2, 5, 6, 11, 12, and 13).

### ***Conclusion***

Many issues related to the inclusion of pregnant women and lactating women in clinical research studies have defied resolution for decades, despite efforts over the years to address them. Among these, concerns about liability faced by researchers and clinicians working within the U.S. healthcare and legal systems are more pervasive than the issue of including pregnant women and lactating women in research alone. While the wide range of perspectives and experience among PRGLAC and ad hoc working group members provided the grounding in reality necessary to develop implementation steps for each of the Task Force’s original recommendations, the working group deliberations made it clear that some issues warrant further and more in-depth discussions.

To avoid becoming mired in issues that are out of the Task Force’s power to solve on its own, the committee took a pragmatic approach to the Secretary’s request to provide guidance on implementation of the PRGLAC recommendations. The Task Force offers 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 in the near future. To achieve this important goal, each of the stakeholder groups represented on the Task Force—government, industry, clinicians, and women—has a critical role in carrying out these implementation steps.

## **PRGLAC Implementation Plan: Recommendation 1**

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

Federal regulatory requirements have posed burdens on the inclusion of pregnant women and lactating women in clinical research, some of which have been addressed. To encourage the appropriate inclusion of these populations in research on therapeutics used during pregnancy or lactation, additional HHS guidance may be needed for the design of ethical studies and IRB approval.

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

In January 2017, HHS and other agencies that have adopted the so-called “Common Rule” regulations for the protection of human subjects in research, issued a final rule to revise and update regulations at 45 CFR 46, Subpart A, the “Federal Policy for the Protection of Human Subjects.” These revisions were implemented in January 2019.

Among the changes to the regulations is the removal of pregnant women as an explicit example of a “vulnerable population” requiring additional ethical scrutiny prior to participating in research. According to the HHS Office for Human Research Protections (OHRP), IRBs will now determine whether pregnant women require additional protections or should not participate in a specific research protocol. Therefore, this PRGLAC recommendation has now been adopted.

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

Although FDA regulations for the protection of human subjects (21 CFR 50) and institutional review boards (IRBs; 21 CFR 56) are nearly identical to the Common Rule, some important differences remain. For example, unlike the revised Common Rule regulations, FDA regulations include pregnant women as an example of a “vulnerable population.” However, the 21st Century Cures Act (P.L. 114-255) requires the FDA to harmonize its regulations with the Common Rule to the extent practicable and consistent with other statutory provisions. FDA’s Office of Good Clinical Practice is leading the ongoing efforts to harmonize the FDA regulations with the revised Common Rule. These efforts are described in the Office of Information and Regulatory Affairs, Office of Management and Budget “Unified Agenda.”<sup>5</sup>

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

Although pregnant women are no longer listed as an example of a “vulnerable population” in the federal Common Rule regulations (45 CFR part 46), developing additional HHS guidance about

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<sup>5</sup> <https://www.reginfo.gov/public/do/eAgendaViewRule?pubID=201804&RIN=0910-AI07>

ethical issues to be considered and strategies for designing ethical studies, to inform the inclusion of pregnant women and lactating women in a clinical trial, may facilitate their participation. Additional information is needed to develop this guidance.

- a. *Determine which studies may require additional consent:* A subset of clinical studies require additional consent from the biological father (45 CFR 46.204(e)), in situations where there is the prospect of direct benefit solely to the fetus versus benefit to the pregnant women or more than minimal risk to the pregnant woman and/or fetus. More detailed information is needed on the studies that do require additional consent, the extent to which additional consent was protective, and quantifying the extent to which participation in the studies is limited due to the extra consent requirements.
- b. *Review existing resources to inform guidance:* The 2018 PRGLAC Report to the HHS Secretary and to Congress provided an extensive summary of federal activities already underway that could, with minor updates, help to inform the development of a guidance document. For example, in 2018, the FDA published a draft guidance, *Pregnant Women: Scientific and Ethical Considerations*, which provides a framework for consideration of inclusion of pregnant women in clinical trials.<sup>6</sup>

In addition, consultation with IRBs that have already implemented the recent changes to the Common Rule regulations would provide valuable input to develop HHS guidance. Many of these IRBs have experience overseeing trials at multiple sites and have approved education plans that could serve as a template. Representatives from these IRBs can provide feedback on including pregnant women and lactating women from the beginning of a clinical trial, or how to manage participants who become pregnant during the study.

- c. *Review federal program experiences to determine successful approaches:* Congress enacted the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) to address the lack of pediatric-specific information in FDA approved therapies. BPCA provides a financial incentive to drug developers in the form of additional marketing exclusivity if they conduct pediatric studies as requested by the FDA; if they decline, the studies may be referred to the National Institutes of Health (NIH) to be conducted under its research program. PREA requires drug developers, under certain circumstances, to assess the safety and efficacy of new drugs and biological products in children. Since these laws were enacted, PREA and BPCA have led to the labeling of over 800 products with pediatric-specific information. The FDA and NIH are charged with administering these programs, which should be evaluated to determine successful approaches that can be applied to research for pregnant women and lactating women. Future programs to stimulate research involving pregnant women and lactating women could be modeled after the applicable approaches under BPCA and PREA.

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<sup>6</sup> <https://www.fda.gov/media/112195/download> ; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design>. When finalized, this guidance will reflect FDA's current thinking on this issue.

- d. *Consider expanding post-market surveillance to capture rare outcomes:* To continue to inform research involving pregnant women and lactating women, and as an added protection for women who use therapeutics during pregnancy or lactation, the FDA could consider expanding post-market surveillance for approved drugs to capture rare outcomes, such as certain birth defects, continuing such reporting throughout pregnancy and lactation. Findings would need to be made available to the public so that the federal guidance for involving pregnant and lactating women in research could continue to be refined.
- e. *How the HHS guidance could facilitate research:* The development by the HHS OHRP of additional HHS guidance would signal that inclusion of pregnant women and lactating women in research, with appropriate protections, is expected. NIH already has policies about inclusion of some sub-populations in research; these could be expanded to include pregnant women and lactating women, ensuring diverse representation by oversampling underrepresented subgroups. With the deletion of pregnant women as a “vulnerable population” from the federal Common Rule regulations, the HHS guidance could serve as a valuable educational document for IRBs and clinical researchers across the country. In addition, such guidance could help set expectations for research collaborations across federal agencies and/or with non-governmental research entities including industry.
- f. *Consider using a central IRB:* Centralized IRBs can apply regulations or guidance in a uniform manner and can develop more in-depth knowledge about working with specific populations, such as pregnant and lactating women, and could also provide expertise in how to mitigate risks associated with pregnancies that may occur during clinical trials. IRBs, including commercial IRBs, with this expertise would be valuable in reviewing clinical trial proposals, particularly multisite trials.
- g. *Education and Oversight:* HHS could consider establishing a central committee or office within the department, similar to the Interagency Autism Coordinating Committee or the National Vaccine Program Office, to oversee educational efforts and applications of regulations and guidance in practice. This central entity could also serve as a resource for future collaborations, including international collaborations and educational exchanges with international IRBs that could augment IRB experience in the United States.



## PRGLAC Implementation Plan: Recommendation 2

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

Pregnant women take an average of five medications during their pregnancies, with little to no evidence for trimester-appropriate dosing, efficacy, or potential adverse event risks. The same lack of dosing information may also hold for different stages of lactation. The vast majority of drugs used by pregnant women and lactating women are not teratogenic. Yet, due to concerns about adverse effects on offspring and liability, decisions about whether to take medications during pregnancy and lactation largely fall on the woman and her healthcare provider. The medical and social cultures need to change to emphasize the potentially adverse effects and serious consequences of withholding treatment from pregnant or lactating women and their offspring versus providing treatment. For example, the transfer of most medications into human breastmilk is less than 5 percent, yet many women who use medications may stop breastfeeding out of concern for their infants. This concern needs to be balanced with possible suboptimal health outcomes for both mother and child of not breastfeeding. Conducting research to increase understanding of disease mechanisms, PKs, and therapeutic responses in pregnant women and lactating women would provide the fundamental information needed to make these culture changes.

Some research efforts funded by NIH or other public funders are underway. However, few studies specifically call for research in pregnant women and lactating women, resulting in insufficient power to inform clinical guidance. Moreover, as a recent review of the research on the effectiveness and potential harms of psychotropic drugs prescribed to pregnant women and lactating women shows, the evidence that exists may be of low quality.<sup>7</sup> A methodical and systematic approach to funding research that focuses on pregnant women and lactating women is needed, including identification of longer term resources. NIH should continue to take the lead in supporting this research in coordination with the FDA, the research community, women's health organizations, industry, and ethical experts.

#### **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**

- a. *Develop a more systematic approach to funding and enhancing research:* A systematic approach to funding research for pregnant women and lactating women would enable studies that are adequately powered and generalizable to inform clinical practice. NIH has invested heavily in infrastructure and data resources that can be leveraged to further research in this area. Existing clinical research networks, such as the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, for pregnancy, or the Pediatric Trials Network

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<sup>7</sup> <http://effectivehealthcare.ahrq.gov/products/mental-health-pregnancy/draft-review>

(PTN), for lactation, with broad experience in recruiting diverse study populations, should receive sufficient funding to facilitate this research and to make the data and biospecimens available to inform future studies through existing repositories, such as NICHD's Data And Specimen Hub (DASH) website. Finding ways to expand access to these networks to early-stage and new investigators and industry partners would multiply the value of these resources.

Since the existing MFMU Network and the PTN are currently supported by NIH, NIH could take the lead on expansion, pending the availability of funding. Funding would be distributed through targeted Funding Opportunity Announcements (FOAs). Development of applications, submission and review, and distribution of funding would take 2 to 4 years, followed by 2- to 5-year research periods. For example, five phase III clinical trials conducted through existing clinical trial networks would cost approximately \$25 to \$30 million, with an additional \$3 to \$7 million for early phase pharmacology studies, and \$5 million for up to 10 mechanistic studies, totaling about \$40 million. Follow-on studies designed to capture longer term maternal and child outcomes would require additional funding.

An additional approach would be to encourage and provide additional support for the inclusion of pregnant women and lactating women in the studies supported by the NIH Clinical and Translational Science Awards (CTSAs) network, which comprises 50 institutions nationwide. This network also could create a training and career development program to understand pharmacologic and therapeutic considerations during pregnancy and lactation research. In addition, training programs in pregnancy and lactation clinical pharmacology could be developed, either as new T32 programs, or as supplemental funding for existing T32 programs (e.g., the Pediatric Clinical Pharmacology Program).

To facilitate recruitment, pregnant women and lactating women should be encouraged to participate in existing registries, such as the PregSource<sup>®</sup> research registry (which includes a medications tracker), condition-based registries (e.g., the Vaccines and Medications in Pregnancy Surveillance System), or industry registries. Additionally, incentives should be created for healthcare providers (including obstetrician-gynecologists [OB-GYNs], nurse midwives, lactation consultants, family medicine, and pediatric offices) to encourage their patients to participate in clinical research studies. A collaboration with Centers for Medicare and Medicaid Services (CMS) could be explored to allow for potential reimbursements to pregnant women and lactating women participating in their programs if they participate in research. (For example, the CMS Innovation Center could conduct a demonstration project to test payment models—such as bundled payments for reimbursements or value-based outcomes—for clinicians serving Medicaid recipients.) In turn, opening these registries to researchers (with appropriate privacy protections for participants) could help inform the development of research hypotheses and facilitate clinical trial recruitment.

NIH, industry, and other funders should also consider new strategies and mechanisms to facilitate innovative ways of conducting research that involves pregnant women and lactating women. Alternative study designs, such as the following, may be useful:

- Comparative effectiveness studies, such as those supported by the Patient-Centered Outcomes Research Institute (PCORI)
- Multi-country clinical trials with endpoints (including surrogate endpoints) that allow for combining the data
- Pragmatic trials
- Cluster-randomized trials
- Clinical trials with adaptive/Bayesian research designs
- Opportunistic and natural history studies
- Big data approaches using Electronic Health Records (EHRs)

These study designs may allow for more effective use of resources and may more efficiently generate evidence to inform decision-making in clinical practice. In addition, the use of telemedicine during the COVID-19 pandemic offers some useful lessons about ways to increase enrollment in studies, online consent, and practices that address obstacles faced by many pregnant women and lactating women, such as rural locations, physical disabilities, transportation, and child care challenges. Current requirements for long-term neonatal follow-up should be expanded to include maternal monitoring at the same time; some of the adaptive design approaches may be useful in determining when a placebo comparison is necessary. If the short-term primary outcome is negative, long-term follow-up may not be needed, thus saving time and funding.

Entities with strong regulatory infrastructure in place are often more successful in conducting research in therapeutic development. A step toward improving regulatory support for the research enterprise is to educate IRBs about the inclusion of pregnant women and lactating women in research. Strengthening the regulatory environment is critical. Investigators with access to a single IRB that is prepared to include pregnant women and lactating women may have more success in moving their studies through the process. Academic research institutions and government funders should seek opportunities to work with industry and the FDA to identify best practices for achieving approval through the regulatory pipeline.

- b. Prioritize the research:* To leverage available resources, a process for prioritizing research is needed that makes a distinction among approved therapies used by pregnant women and lactating women, new therapies (in development) that could be used in pregnant women and lactating women, and new product development for pregnancy- and lactation-related conditions. Outlining the basic science discoveries that would facilitate

targeted testing of future interventions would make the prioritization process more efficient.

Establishing the BPCA prioritization process took about 2 years and has been refined periodically since the first priority list was published. A similar timeframe would be expected to establish a similar process for prioritizing research on pregnant women and lactating women (see also Recommendation 8).

- c. *Expand the availability of preclinical models:* To address the issue of regulatory concern about the potential safety of therapeutics used by pregnant women and lactating women, additional preclinical models and methods should be developed to augment traditional reproductive/toxicity studies and provide evidence of safety and efficacy during different stages of pregnancy. Current preclinical (animal) models have limitations for extrapolating the findings to humans. *Ex vivo* placenta perfusion studies can only be performed after the placenta has been delivered, and therefore provide information on transport and metabolism only in late pregnancy results. Consequently, to advance research in therapeutics in pregnancy, support for additional preclinical models is essential. Consulting with organizations that conduct preclinical safety research according to international guidelines may be helpful. Preclinical models for testing drugs during lactation should reflect the different stages of lactation (i.e., the transfer of drugs during Lactogenesis 1 versus Lactogenesis 2). A first step would be to form a working group of relevant NIH Institutes and Centers (ICs), FDA representatives, researchers, and industry representatives to decide which new *in silico*, *in vitro*, and/or animal models are optimal for each disease or condition experienced during pregnancy or lactation, and to establish agreement on the amount and type of preclinical work required. Once determined, these findings should be published widely in relevant journals and on government websites. This process, which could be facilitated by the FDA-NIH Joint Leadership Council, could be completed within 2 years, requiring appropriate staff time and administrative costs.
- d. *Maximize the usability of data:* To ensure that the data gathered are clinically meaningful, common data elements and outcome measures first need to be developed and validated. The same working group described earlier, or another similarly constituted group working in collaboration with the preclinical group, should work toward agreement on surrogate or clinically meaningful endpoints for safety and efficacy for research involving the use of therapeutics by pregnant women or lactating women. Determination of acceptable endpoints will determine the sample sizes and duration of clinical trials. With input from ethicists, this group would also be charged with coming to agreement regarding risk/benefit guidelines for clinical trials involving pregnant women and lactating women. The group could also consider principles for finding the balance between risk to the women and to the fetus/infant from absence of treatment compared to risk to the fetus/infant for congenital anomalies or other adverse outcomes from exposure to the drug. The establishment of a working group could occur within a year if all relevant parties are available.

Collaborations and partnerships should be created with industry, philanthropic, and global partners, such as the Innovative Medicines Initiative on Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology, and Breastfeeding to Improve Outcomes Now (IMI 2 ConcePTION) initiative, a public-private partnership between the European Union and the European pharmaceutical industry to develop the next generation of vaccines and medications for pregnant women and lactating women. The goal of the partnership is to create a pan-European system capable of providing evidence-based information on the safety of medications used during pregnancy and lactation, augmenting and leveraging research data and resources. Additional collaborations should be established with EHR companies and other organizations that use secondary analysis data methods using big data sources to identify potential signals and trends within such datasets, identify eligible participants for clinical registries and translational and clinical studies, and develop best practices for EHR-based studies. Initial discussions about potential collaborations with IMI 2 ConcePTION already have taken place with PRGLAC leadership.

- e. *Develop new research tools:* New types of research tools would facilitate understanding of the effects of therapeutics used by pregnant women and lactating women. For example, new tools and methods that assay therapeutic products in blood and human breastmilk, such as those that utilize small volumes and are sensitive to detect minute quantities, are needed to understand more thoroughly the quantity of drug that passes through human breastmilk.

Additional tools are needed to assess more precisely pharmacokinetic (PK) and pharmacodynamic (PD) responses in pregnant women, lactating women, and infants. The development of *in vivo* and *in vitro* systems for product testing would provide noninvasive ways to predict safety and effectiveness. In addition to ongoing placental research (such as NICHD's Human Placenta Project), new methods (e.g., measuring brain development via MRI or levels of metabolites in fetal liver or blood) are needed to evaluate the fetus more effectively under various clinical conditions. For example, at least one academic institution is developing "tissue-on-a-chip" to test the toxicity of chemicals on mammary tissue, potentially reducing the need for cell cultures that may not adequately mimic how the substance would work in the human body. These "tissue-on-a-chip" approaches would expand the range of usable models, adding to the tools available to researchers. The Bill and Melinda Gates Foundation is funding the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom to create a repository of information for assessing drug exposure in pregnancy, including PK modeling.

The development of these tools should proceed on an ongoing basis. Adding them to the research arsenal, either through NIH-sponsored research opportunities, or a public-private partnership, could efficiently move the field forward.

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

Due to challenges in recruiting pregnant women and lactating women for studies on therapeutics, limited, targeted funding opportunities that permit longer term awards would ensure that clinical studies can recruit sufficient numbers of participants to inform clinical practice, especially for studies that address complex clinical issues. A related approach is to encourage issuance of “phased” awards to allow pre-clinical trial activities to be completed in up to 3 years; then, if that phase is successful, the study can transition to the more typical 5-year award for the trial itself. While NIH does not prohibit awards beyond the standard 5 years, these types of awards are still relatively rare. NIH also frequently permits “no-cost extensions,” which allow grantees to complete clinical research within a year or 2 beyond the original 5-year award period. Selected programs, such as NICHD’s PTN, are funded through contract mechanisms for longer periods to accommodate clinical trials. Having dedicated funds, such as for the INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) initiative, would provide needed impetus to the research field.

Funding a network of researchers for longer periods, i.e., allowing networks to perform studies that span more than one funding cycle, would save the time used to create the infrastructure needed for clinical trials, and allow the conduct of a follow-up study, which is often required to assess long-term outcomes for either the woman or her fetus/infant. Currently, awards can be distributed within 2 to 4 years from concept, through FOAs, review, and distribution, with the research itself completed within 3 to 5 years, possibly followed by a no-cost extension.

## **PRGLAC Implementation Plan: Recommendation 3**

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

The dearth of researchers and clinicians with expertise in obstetric and lactation pharmacology necessitates significant investment and targeted programs, including dedicated training, mentorship, and educational opportunities, as well as continuing education for established clinicians in order to advance the field. For example, established research networks can be leveraged to provide some of these opportunities. Likewise, expanding the range of programs available to interested trainees and public-private partnerships among academia, industry, government, women's health organizations, or professional societies should be explored.

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

- a. Types of training programs:* A critical component of any expansion of research in obstetric and lactation pharmacology and therapeutics is a workforce trained with the necessary expertise. Relevant disciplines include PK, PD, pharmacogenomics, and pharmacoepidemiology, as well as pediatric bioethicists. Lessons can be learned from the field of pediatric pharmacology, which was in a similar situation three decades ago.

NIH currently supports multiple programs and mechanisms that could be utilized or expanded to incorporate training in obstetric and lactation pharmacology:

- Dual fellowship programs, utilizing the T32 mechanism (for example, concurrent maternal-fetal medicine and T32 clinical pharmacology fellowships), to encourage trainees to submit career development (K) award applications for funding, and subsequently develop an independent research career
- K99/R00 awards to support continued career development
- KL2/K12 awards to fund newly trained clinician scientists, such as NICHD's Women's Reproductive Health Research Career Development Program for OB-GYN research trainees
- R37 Merit awards, providing long-term support for superior performance
- Diversity supplements to incorporate obstetricians and maternal-fetal medicine specialists, those from under-represented backgrounds in science, and those who will be serving under-represented populations, into training efforts
- Administrative supplements for ongoing grants to support additional research in obstetric and lactation pharmacology and therapeutics
- Dedicated loan repayment programs for clinicians and researchers who are (or will be) involved in obstetric and lactation pharmacology and therapeutics

To date, some K training awards have been made, largely to prior T32 awardees from the National Institute of General Medical Sciences in clinical pharmacology. In addition, FOAs were issued by NIH in 2010 and 2011, with six training awards made.

*b. Additional training opportunities:* To expand the availability of training opportunities, other training programs should be established to help increase expertise and stimulate research in obstetric and lactation pharmacology and therapeutics. As these training opportunities are being established, particular attention should be paid to supporting a diverse group of investigators.

- Clinical pharmacology certification programs to help those with clinical expertise and/or pharmacology backgrounds receive additional, rigorous training in this specialty with a less burdensome time commitment than obtaining an advanced degree, with particular attention to increasing diverse representation in the research
- Creation of dedicated training tracks within NIH-supported centers of excellence and existing research networks (e.g., the MFMU Network or the CTSA program); in addition to training in obstetric and lactation pharmacology and therapeutics development, this approach would provide trainees with greater access to appropriate research participants.
- Establish collaborations between government funders and industry partners to offer short-term fellowship opportunities in obstetric and lactation pharmacology and therapeutics development; cost-sharing could be considered
- Create new internship programs within the NIH Clinical Center or the FDA

For example, NICHD has funded a study through its PTN (20 sites) to evaluate off-patent drugs in lactating women and their infants. This project could be leveraged and expanded so that trainees interested in lactation research can gain experience.

The establishment of new training mechanisms or funding opportunities at NIH takes, on average, 1 to 3 years. With dedicated effort, integrating obstetric and lactation pharmacology and therapeutics into clinical trial protocol development is estimated to take between 3 and 5 years.

*c. Addressing challenges:*

- Frequently cited problems for research trainees include low salary caps, lack of protected time for research, and malpractice insurance for both clinician/scientists and non-clinician investigators. To encourage academic institutions to engage in these types of training program, the NIH or other funder should consider allowing trainees with K career development awards (NIH-supported grant awards that provide individual and institutional research training opportunities) to reduce the amount of required research time or providing additional funding to offset salary when significant amounts of time are needed, mitigating the financial impact on the



institution and increasing the number of awards that could be made. NIH could also consider developing different types of K awards with varying levels of protected time required.

- Ensure that review panels have the appropriate expertise to review training grant application that include provisions for protected research time.
- To encourage promising trainees with diverse backgrounds to consider careers in obstetric or lactation pharmacology, establish or augment a clear training career path including avenues of support post-training.
- Strengthen the infrastructure for conducting PK/PD studies by establishing or expanding a dedicated network or cohort of core labs in obstetrics and lactation pharmacology and therapeutics testing and development. Such an infrastructure would ensure that well-trained personnel and appropriate equipment are available to conduct the testing and interpret results. A core lab could also accept and analyze samples from other studies, serve as a consultant on protocol design, and provide mentorship for trainees.

*d. Strategies to increase awareness of career opportunities:*

- Multiple opportunities for recruitment and awareness exist at professional society meetings (e.g., Society for Maternal-Fetal Medicine [SMFM], the American College of Obstetricians and Gynecologists [ACOG], the Association of Women's Health, Obstetric, and Neonatal Nurses, and the American College of Nurse Midwives, among others). Organizations that already have relevant courses available may be willing to partner; these may include the Society for Birth Defects and Research Prevention (formerly the Teratology Society) and Organization of Teratology Information Specialists (OTIS), which has a course on how to develop study protocols that make use of a human breastmilk biorepository.
- Additional awareness efforts could be tailored to medical schools and schools of pharmacy, such as the American Association of Colleges of Pharmacy and the Association of American Medical Colleges, beginning with their member organizations.
- Other stakeholders with an interest in training in obstetric and lactation pharmacology and therapeutics include other federal agencies, such as FDA, the Centers for Disease Control and Prevention (CDC), CMS, the Agency for Healthcare Research and Quality (AHRQ), the Health Resources and Services Administration (HRSA), and credentialing organizations, nonprofit funders, and industry.

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

- a. Increasing support for mentors:* NIH has several grant award mechanisms (R37 Merit awards, K24 career development awards, or salary support through existing clinical

research networks) that provide necessary salary support so that mentors can afford time away from their other responsibilities. The current requirement for 50 percent of a mentor's time could be reduced, or other incentives provided, to encourage more established clinical researchers to serve as mentors. In addition, the criteria for reviewing training grants, such as the T32 awards, could be amended to recognize the value of quality improvement in this area.

Establishing new mentorship programs or amending current programs could take 1 to 2 years.

- b. Helping mentees find mentors:* To support mentees' identification of potential mentors, a virtual "college of mentors" could be created, especially in newer areas such as obstetric and lactation pharmacology and therapeutics. Sources for "faculty" mentors could be principal investigators on current NIH-funded studies within the PTN and other networks. In addition, cross-disciplinary mentoring—for example, pairing an obstetrician or nurse-midwife with an epidemiologist or pharmacist—could provide additional educational benefit.

Establishing and recruiting a virtual college of mentors could take 1 to 2 years; however, increasing the incentives for participation may take longer.

- c. Training on FDA requirements and processes:* Training modules for both mentors and mentees on FDA regulations for product development and approval processes would facilitate a broader understanding of all aspects of obstetric and lactation pharmacology and therapeutics research. In addition, FDA and NIH could hold clinical investigator educational sessions focused on clinical research in obstetric and lactation pharmacology. The FDA also has offered sabbatical programs with academic institutions to provide specialized research opportunities.

### **3C. Increase the knowledge and engagement of healthcare providers regarding obstetric and lactation pharmacology and therapeutics**

- a. Changes to educational requirements:* Accreditation and credentialing bodies, professional societies, board-certification organizations, hospital groups, payers, and continuing education entities should be encouraged to include content in educational programs and for board licensures to help train healthcare professionals about clinical research and pharmacology related to pregnancy and lactation, including an overview of different research methods that can be used in studying these populations. All relevant professionals, such as nurses, advanced practice nurses, (including nurse-midwives), lactation professionals, pharmacists, and physicians (OB-GYNs, maternal-fetal medicine specialists, pediatricians), should be included. Avenues for this training include continuing medical and nursing education programs, Medscape tutorials, and Maintenance of Certification Programs for Allied Health Professionals.

- b. *Creating training opportunities:* Providing easy, online training opportunities would increase the knowledge base of healthcare professionals and researchers in PK, PD, pharmacogenomics, and pharmacoepidemiology. Working with specific professional societies to incorporate this information into existing educational vehicles would be a cost-effective way of increasing awareness. For example, ACOG and SMFM sponsor webinars and retreats for their fellows that could include talks on obstetric and lactation pharmacology and therapeutics. NIH's BPCA program also hosts regular webinars on pharmacology research, and the NIH Principles of Clinical Pharmacology online course could be advertised more widely to healthcare professionals. Fellows who must complete theses during their training to become board-certified could be encouraged to focus on PK/PD studies in pregnancy and lactation.
- c. *Electronic Medical Record (EMR) modules:* Some EMR modules exist to help healthcare providers identify eligible participants for clinical trials. These modules could be expanded to include identification of women who are pregnant or lactating, and to provide training on how to recruit these populations for clinical research purposes.

The creation of new programs to engage healthcare providers could take 1 to 3 years, pending available funding. Integration of new programs and/or information about obstetric and lactation pharmacology and therapeutics, and inclusion of pregnant and lactating women in clinical research into accreditation or credentialing systems is estimated to take 3 to 5 years.

## PRGLAC Implementation Plan: Recommendation 4

### *Rec. 4. Remove regulatory barriers to research in pregnant women*

#### **4A. Modify subpart B of the Common Rule:**<sup>8</sup>

- **Change 46.204(e)<sup>9</sup> 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 help benefit the child and to align with parental consent for pediatrics**
- **Add in the option of “Minor increase over minimal risk” from subpart D to 36.046<sup>10</sup>**

(*Note:* FDA regulations for the protection of human subjects Subpart D: Additional Safeguards for Children in Clinical Investigations, 21 CFR 50.51-54; subsections 50.51 (research involving minimal risk) and 50.52 (prospect of direct benefit) require consent from one parent for participation in research; subsections 50.53 (minor increase over minimal risk and no prospect of direct benefit) and 50.54 (not otherwise approvable) require both parents’ consent. FDA regulations align with the HHS parental consent requirements in subpart D: Additional Protections for Children Involved as Subjects in Research (45 CFR 46.404-407).)

- Collect data to inform proposed rulemaking:* Information on the burden, if any, that current regulatory requirements pose for researchers should be collected and applied. For example, how many pregnant women currently are being denied the ability to participate in studies that hold out the prospect of direct benefit solely to the fetus because of the requirement to obtain consent from the biological father? In some cases, changes in family structure may pose major obstacles to obtaining consent from both biological parents; consequently, collection of demographic information would provide needed context. In addition, data on inclusion of specific subpopulations would help to ensure that a diversity of pregnant women and lactating women are included in research.
- Encourage OHRP to initiate rulemaking:* Women are not cognitively impaired during pregnancy and are capable of making informed decisions. OHRP should be encouraged to initiate the rulemaking process to modify subpart B of the HHS regulations. Rulemaking involves an extended process that incorporates public notice and the

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<sup>8</sup> The bolded text represents the original recommendation made by PRGLAC in the 2018 Report to the Secretary. PRGLAC wishes to note that technically, subpart B is not considered part of the Common Rule; that is limited to subpart A of the regulations on the protection of human subjects. The correct references have been used throughout the text of the PRGLAC Implementation Plan.

<sup>9</sup> 45 CFR 46.204(e)

<sup>10</sup> See explanatory note above for more complete references to subpart D of the regulations.

opportunity for public comment.<sup>11</sup> In addition, in the past, OHRP has considered findings from pilot studies prior to issuing a proposed rule or rule change.<sup>12</sup>

- c. *Convene experts to define what constitutes “minimal risk” for a pregnant woman and fetus:* Prior to recommending changes to language on “minor increase over minimal risk” for subpart B to mirror subpart D, experts and stakeholders should be convened to reach consensus on the definition of what constitutes a minor increase over minimal risk for both the pregnant woman and the fetus. (For example, a clinical study of an approved drug with available safety data suggesting no identified risk in nonpregnant women, along with reproductive toxicology studies that do not identify any risks.) When consensus around this definition and potential impact is reached, OHRP should be encouraged to initiate the rulemaking process to further modify subpart B, seeking a broad range of input from the research community and the public.

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<sup>11</sup> [https://www.federalregister.gov/uploads/2011/01/the\\_rulemaking\\_process.pdf](https://www.federalregister.gov/uploads/2011/01/the_rulemaking_process.pdf) and <https://www.hhs.gov/ohrp/regulations-and-policy/index.html>

<sup>12</sup> <https://hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-return-individual-research-results/index.html>

## PRGLAC Implementation Plan: Recommendation 5

### ***Rec. 5: Create a public awareness campaign to engage the public and healthcare providers in research on pregnant women and lactating women***

For any cultural shift to occur, the associated behavioral change requires a targeted communications strategy. When communicating information relevant to treating pregnant women and lactating women, messages must be concise, consistent, tailored, and actionable for women and their healthcare providers. For example, researchers, IRBs, professional societies, and healthcare providers may not be fully aware of the recent changes to the federal regulations for the protection of human subjects, e.g., the Common Rule, or particularly the removal of pregnant women as an example of a “vulnerable population.” Merely increasing awareness of this change may encourage academic investigators to include pregnant and lactating women in studies of drugs and other therapeutics. The 2018 PRGLAC Report to the HHS Secretary and to Congress alerted many within the public health and research communities to these changes and their potential implications, but far more needs to be done.

#### **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**

- 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:* The needs assessment could identify reasons for the lack of effective communication about this issue, such as barriers to this research, program and budgeting priorities, lack of resources, lack of capacity or expertise, and a complete understanding of the value of participation. Agencies and organizations that have experience with public awareness campaigns should collaborate to identify best practices, particularly in creating effective messaging to reach a diverse range of audiences. These organizations would also be helpful in clarifying what information gaps for their audience(s) should be addressed by a public awareness campaign, including identification of possible actions to fill those gaps.

A formal needs assessment could be conducted, whether in-house within a federal agency, or through a request for proposals to obtain additional expertise. An alternative approach would be to develop a public private-partnership that could include industry, the Foundation for the NIH (FNIH), academia, and other private sector partners to examine the knowledge gaps, barriers and facilitators, and support a campaign related to current, commonly used medications or therapeutics in pregnant and lactating women.

An environmental scan to determine what resources already exist would prevent duplication and ensure consistent messaging. Some organizations have already developed messaging and materials specific to some exposures and medications (e.g.,

pregnancy studies at <http://mothertobaby.org>) or conditions (e.g., <http://ibdparenthoodproject.org>). The FDA publishes a list of pregnancy exposure registries (<https://www.fda.gov/science-research/womens-health-research/pregnancy-registries>), which are included at the drug sponsor's request. These, along with available medication safety references, could be useful resources in the development of a public awareness campaign aimed at behavior change.

Completion of a needs assessment, environmental scan, and preparation for a campaign could take an estimated 2 years.

- 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:* A logic model, similar to that used by NICHD's Safe to Sleep<sup>®</sup> public education effort, is a useful way to organize activities related to public health awareness and should be considered for implementation of this PRGLAC recommendation. Such a model may include the following components:
- Inputs: collaborators, partners, and materials that will be needed
  - Activities: research agenda and the collaborations needed to create evidence-based communications, which are used to promote awareness, overcome barriers to effective communication about research participation, and plan for periodic monitoring and evaluating outcomes and impact in order to adjust and refine the strategy
  - Target audiences and tailored messages (see 5Ac): for example, for a healthcare provider audience, messages may include training on how to enroll underrepresented populations
  - Short-term outcome measures: changes to knowledge, attitudes motivation, processes, and resource allocation
  - Intermediate outcome measures: behavior change (e.g., enrollment rates of pregnant women and lactating women in clinical research)
  - Long-term outcome measures: availability and quality of safety/efficacy/dosing information specific to pregnant women and lactating women
- c. *Pilot tailored risk communication messaging for each stakeholder audience:* Different stakeholder audiences may have differing concerns about the inclusion of pregnant women and lactating women in research. These concerns must be addressed directly in the development of any educational effort/messaging intended to reach each audience, including federal policymakers; healthcare providers (including but not limited to clinicians, pharmacists, lactation consultants, dietitians, nursing and allied health professionals, nurse midwives, nurse practitioners); academic and industry researchers; medical, health, and pharmacy associations; teratology information specialists and genetic counselors; and pregnant women and lactating women and family members from

a variety of socioeconomic, cultural, and educational backgrounds, possibly through organizations representing women's and family health interests, such as doula and social work organizations. For example, the National Heart, Lung, and Blood Institute (NHLBI) supports a website on the importance of including children in clinical studies that provides a potential model for participant and family audiences.<sup>13</sup> The site includes videos and other information targeted to potential study participants and their families.

Equally important is to convey both the potential health and safety risks of foregoing therapies for conditions experienced during pregnancy or lactation or not using dosages of those medications, biologics, or other therapeutics that are safe and effective. To assist in illustrating these issues, educational efforts need to include real-life stories about pregnant or lactating women's experiences to illustrate absolute risk, relative risk, and the trade-off of risks and benefits. These stories may include the consequences of stopping treatment for ongoing conditions, failure to treat emerging conditions, and unintended incorrect dosing due to the physiological changes during pregnancy. Once developed, these messages should be pilot tested to ensure comprehension and acceptability prior to being rolled out to a wider audience.

For example, despite the long-term benefits of breastfeeding, the lack of data on medications that may be prescribed for lactating women often results in recommendations against breastfeeding for women who require therapeutics for medical reasons. Until more studies on medications used by lactating women are completed, the interim messaging to women and their healthcare providers may only reflect that data are lacking, and that they must balance risks and benefits of medication use with continuation of breastfeeding.

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

- a. *Keep core messaging simple and consistent:* Although messaging should be developed for specific audiences, the core message around the importance of inclusion of pregnant women and lactating women in appropriate clinical and non-clinical research should be consistently maintained.
- b. *Determine effective methods to reach each audience:* Building on that core messaging, developing a targeted awareness campaign requires working with each intended audience to identify which methods will best reach them, such as trusted websites, professional society publications or announcements, and direct communications from leadership or funders. Women's health and population-oriented organizations can also play a leading role in conveying evidence-based information to various racial, ethnic, and cultural groups. This campaign could also include a woman-centered decision support tool that

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<sup>13</sup> <http://www.childrenandclinicalstudies.org>



helps to translate the available evidence on risks and benefits of a therapeutic to assist women and their healthcare providers in making those decisions.<sup>14</sup>

- c. *Develop action plans for each audience:* Using the logic model described earlier, a plan for conveying “call-to-action” messaging to each stakeholder group (e.g., healthcare professionals, industry, women’s health organizations, researchers) about inclusion/participation of pregnant women and lactating women in research could be developed. Such plans should outline training on how to enroll racially, ethnically, and culturally diverse groups of women into clinical studies; the materials and resources that will be needed (e.g., design, budget, and schedule for updates); how the materials and messages will be disseminated; and how to evaluate progress on reaching those audiences.

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<sup>14</sup> Krista F. Huybrechts, M.S., Ph.D., “Benefit-Risk Trade-off for Psychiatric Medications in Pregnancy,” presented May 20, 2020, Pregnancy and Maternal Conditions That Increase the Risk of Morbidity and Mortality Workshop: <https://videocast.nih.gov/watch=36363>

## PRGLAC Implementation Plan: Recommendation 6

### ***Rec. 6. Develop and implement evidence-based communication strategies with healthcare providers on information relevant to research on pregnant women and lactating women***

Despite the widespread use of the internet for healthcare information, studies repeatedly show that healthcare providers remain a trusted source of information about health.<sup>15</sup> Consequently, healthcare providers are often asked to convey public health messages and research findings to their patients in lay language. They also serve as a *de facto* gatekeeper for approaching pregnant women and lactating women about enrollment into research studies. Any hesitation on the part of the trusted healthcare provider about participation diminishes the chance of engagement of his or her patients in research, even when participation could provide direct benefit to the women. Increasing healthcare providers' knowledge about obstetric and lactation research needs, training on how to approach a diverse group of women regarding participation, and comfort with discussing clinical trials or other studies (such as pregnancy registries or lactation studies) and enrolling their patients, as appropriate, will reduce this barrier to increased research participation.

#### **6A. Increase the knowledge of healthcare providers regarding obstetric and lactation therapeutics and research needs**

- a. *Foster two-way communication between the research community and healthcare providers about obstetric and lactation therapeutic research needs:* Funding agencies, professional societies, and organizations representing the research community should create a forum, such as a conference, for dialogue to identify obstetric and lactation therapeutic research needs, both from the research perspective as well as clinical observations from practicing healthcare providers. Results from this forum, which could include a listing of research needs, could be published and disseminated widely. This forum could also serve as the basis for an ongoing effort to keep the list of research needs updated and further foster communications (see also Recommendations 3C and 2Ae).
- b. *Increase healthcare providers' awareness of obstetric and lactation therapeutic research needs:* Establish additional avenues (or make current avenues more accessible) for healthcare providers to easily obtain information about available clinical trials and other studies, such as pregnancy registries and lactation studies, and information on recent trial or study results. For example, a regularly scheduled podcast with research updates or partnership with a journal could help raise awareness. This effort could be one component of the overall public awareness campaign geared toward healthcare providers (see Recommendation 5), which could include a needs assessment of healthcare providers' baseline knowledge.
- c. *Encourage healthcare providers' engagement by increasing continuing education opportunities:* Stakeholders, including but not limited to federal agencies, with expertise

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<sup>15</sup> <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/766849>

in research related to therapeutics used by pregnant women and lactating women could partner with leading professional societies that serve the healthcare provider community to create continuing medical education (CME) modules that would be linked to maintenance of board certification or licensure. In addition to content about current knowledge of the therapeutics used by pregnant women and lactating women, these modules should explain how to access and how to communicate this information to a diverse group of potential participants, including information about balancing the risk of taking a medication with that of not treating an underlying condition. Once CME modules have been developed, stakeholders could work with state boards that oversee medical, nursing, pharmacist, and other healthcare provider continuing education programs to add a requirement for this area (similar to current requirements for opioids and pain management) (see also Recommendation 3).

## **6B. Increase the engagement of healthcare providers to disseminate information from research findings to their patients**

- a. *Maximize existing resources, adapting for use by healthcare providers and their patients:* Healthcare providers could be regularly informed about the availability of existing resources that translate clinical research findings into accessible language for patient discussions on therapeutics used during pregnancy and lactation. Creation of a central web location/app with a compilation of these resources would likely be well utilized and could be accomplished within 2 years. A government agency involved in PRGLAC could verify that the resources listed in the compilation are based on valid clinical evidence.

For example, in 2014, the FDA published the final Pregnancy and Lactation Labeling Rule (PLLR) to improve on the clarity of information that is included in prescription product labeling related to pregnancy and lactation. The PLLR is intended to provide a better description of the available data gleaned from clinical studies to inform both prescribers and their patients about the risks of using the drug during pregnancy and lactation so that they can make better risk-benefit decisions. Over 1000 products have been converted to this format (see <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

- b. *Partner with professional societies to facilitate healthcare providers' knowledge of and access to information about research findings relevant to pregnant and lactating women:* Organizations representing researchers in this field and agencies that support their work could partner with professional societies and their communications offices to make these informational resources on therapeutics used during pregnancy and lactation easily available to their membership. Among the products these partnerships could produce could be easily downloadable handouts written for a lay audience for healthcare providers to share with their patients. Examples of such materials already exist and could serve as

models for new materials on therapies used during pregnancy and lactation.<sup>16</sup>

In addition, encouraging publication of research findings on PK, pharmacogenetics, and other considerations in pharmaceutical therapies for pregnant women and lactating women in journals with an intended audience of clinicians and researchers who work in obstetrics (including maternal-fetal medicine). Such publications, or co-published commentaries, should discuss the clinical implications of research findings, as appropriate. These publications could offer CME credits along with these articles.

- c. *Partner with professional societies to facilitate healthcare providers' knowledge about clinical trials on therapeutics in pregnancy and lactation:* Healthcare providers need an up-to-date resource to quickly access information about relevant clinical trials and to offer to their patients who may have health conditions during pregnancy or while breastfeeding. In addition to publications in journals on research results from relevant clinical trials, information about trials seeking to recruit in professional society newsletters and presentations at annual meetings of these societies (which could also include CME credits) could increase awareness of the types of trials that may be available. For example, the [clinicaltrials.gov](http://clinicaltrials.gov) site could be updated to become more accessible to healthcare providers and the lay public<sup>17</sup>, creating a function that would allow listed trials to be sorted geographically or by institution. An easily accessible app could be developed and targeted toward the type of information that healthcare providers can pass along to their patients.

## **6C. Increase the engagement of healthcare providers to discuss participation in clinical trials, research, and registries**

- a. *Establish and maintain a readily accessible website to increase awareness of clinical research opportunities:* This site would serve as a central location for information on how to find and participate in a clinical trial and/or a research registry that uses language appropriate to potential participants. For example, the NIH's "Clinical Research Awareness and You" website is aimed at individuals and family members who may be considering participation in a NIH-funded clinical trial, including commonly asked questions and answers about clinical trials, testimonials from participants, a list of vetted research registries, and links to [clinicaltrials.gov](http://clinicaltrials.gov) and other resources. Healthcare providers could point their patients to these sites and use them to explain clinical trial participation.

Alternatively, a comprehensive listing of websites and other resources, including links to similar public and private sector resources about clinical trial participation, could be posted on each agency's and organization's website and disseminated widely. This

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<sup>16</sup> <https://cdc.gov/vaccines/pregnancy/hcp-toolkit/resources-patient-education.html>; <https://acog.org/store/products/patient.education>; <https://lactationtraining.com/resources/educational-materials/handouts-parents/handouts-lactation>; and <https://safetosleep.nichd.nih.gov/materials>

<sup>17</sup> The National Library of Medicine, which oversees [clinicaltrials.gov](http://clinicaltrials.gov), is currently modernizing the site.

listing should include links to military health systems used by Department of Defense (DoD) and the Department of Veterans Affairs (VA).

- b. Assist healthcare providers in finding time for discussions with patients about participating in research:* Developing a video for dissemination to professional societies and organizations that represent healthcare providers would prevent having to use a provider's limited appointment window for conversations about research participation. This video, which would explain the importance of conducting research on therapeutics used by pregnant women and lactating women, could provide updated information on regulatory issues (the revised Common Rule regulations; FDA guidances<sup>18</sup>) and address likely questions that healthcare providers may have about suggesting that their patients may want to consider enrolling in clinical trials or research registries. The NHLBI/NIH-developed video about pediatric participation in clinical trials may serve as a model.<sup>19</sup>

In addition, other staff members in a healthcare setting could be empowered to discuss studies that may be relevant to particular patients and serve as resources for follow-up questions. The EHR notification system could invite a pregnant or lactating woman to indicate whether she would be interested in discussing research participation at her next appointment. Community outreach efforts also would encourage potential participants to inquire about studies when they come for their appointments.

- c. Explore incentives for healthcare providers to discuss clinical trials with their patients:* Convene a roundtable forum with representatives of healthcare provider groups to:
- 1) identify the barriers that prevent healthcare providers from engaging with pregnant women and lactating women in discussions about clinical trial participation, and
  - 2) potential strategies for reducing those barriers, such as continuing education credits and prepared educational materials. Behavioral incentives, such as formal feedback that gives credit to healthcare providers for getting their patients involved in trials, or grading metrics from payers, should also be included in this discussion. Alternatively, or in conjunction with a forum, a PRGLAC member federal agency could publish a Request for Information asking for similar input (see also Recommendation 2).
- d. Include healthcare providers in planning for clinical trials:* Investigators designing clinical trials that could include pregnant women and lactating women should consult with healthcare providers while planning these studies on issues such as time and costs of recruitment. Research funders could require that clinical trial preparation include consultation with healthcare providers on obstetric and lactation research needs they encounter.

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<sup>18</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnant-women-scientific-and-ethical-considerations-inclusion-clinical-trials>

<sup>19</sup> <http://www.childrenandclinicalstudies.org/>

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

- a. Identify and reduce costs that may pose barriers to accessing information:* Updated research findings are largely available through subscriptions to professional journals, books, and other resources, such as product labeling. Various stakeholders (professional societies, funders) should explore strategies for making those results more widely available to practicing clinicians who see pregnant women or lactating women. Newsletter articles published by societies and women’s health organizations, summary issue briefs posted online by federal agencies, and presentations at meetings hosted by stakeholders are viable options for providing access to this information and helping to interpret relative risks and benefits of therapeutics. One approach is the Knowledge SUCCESS (Strengthening Use, Capacity, Collaboration, Exchange, Synthesis, and Sharing) program, funded by the U.S. Agency for International Development, which uses a systematic approach to help healthcare organizations collect and organize information to make it easier for people to use.<sup>20</sup>
- b. Share research results with participants and their healthcare providers:* Clinical trial participants often report that a major reason they commit to participating and completing a clinical trial is that they will receive results, either individually, for the overall outcome, or both. Summaries of completed trials should be written in language(s) accessible to the participants and posted in a central location, such as [clinicaltrials.gov](http://clinicaltrials.gov). One potential model for these summaries are those posted by PCORI.<sup>21</sup> The IMI 2 ConcePTION project is developing a model for disseminating research findings, in multiple languages, and could be a valuable partner in this effort. Another approach is to share research results through webinars open to academic and industry researchers, such as NICHD’s Sumner J. Yaffe webinar series.
- c. Explore mechanisms by which to appropriately share data:* In addition to disseminating research results as described earlier, researchers, potential funders, and professional societies considering changes to clinical guidelines may wish to examine the data from these studies. Various approaches to sharing these data should be considered, such as a public website requiring registration and use of unique identifiers so that personal health information is not released. As data are shared, appropriate caveats should be included if they are insufficiently conclusive. The FDA’s Sentinel Initiative, a repository for retrospective data, is a national electronic system that allows researchers to monitor the safety of FDA-regulated medical products, including drugs, vaccines, biologics, and medical devices. This system complements existing FDA surveillance capabilities that track adverse events of FDA-regulated drug products.

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<sup>20</sup> <https://knowledgesuccess.org/what-we-do/>

<sup>21</sup> <https://www.pcori.org/research-results-home>

## **PRGLAC Implementation Plan: Recommendation 7**

### ***Rec. 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***

Although PRGLAC is not in a position to address the overarching tort reform and liability issues that are part of our legal system, the Task Force can suggest some interim steps that could contribute to the ability of researchers to include pregnant women and lactating women in their studies of drugs and other therapeutics. Some of these steps are based on successful attributes of existing programs and approaches to research.

#### **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**
  - 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:* Specifically, this panel should include individuals with legal expertise at the federal and state levels; regulatory expertise; plaintiffs' attorneys; pharmaceutical representatives with tort liability and research expertise; insurance industry representatives; federally funded researchers who work with pregnant and lactating women; and health policy experts. With agency support, the National Academies of Sciences, Engineering, and Medicine could be considered as a convener of such a panel.

The panel's charge would be to develop a matrix with relative liability for: 1) currently on-market and off-patent therapeutics; 2) currently on-market and on-patent therapeutics; and 3) new therapeutics under development. The liability risks to pharmaceutical companies, individual researchers and their institutions, and the government for conducting research specifically on therapeutics for medical conditions experienced by pregnant women and lactating women should be considered (see Figure 1). In addition, the panel should distinguish between liability issues for pregnant women separately from lactating women in the matrix or develop separate matrices for these two groups because the liability profiles differ. Gaps in the data are extensive for both groups.

As a first step, the panel would conduct an analysis of the myriad of state laws and regulations governing liability for conducting research, including informed consent provisions, and to which populations they apply.

After conducting the analysis and developing the matrix described earlier, the panel would make recommendations for conducting research that substantially mitigates or avoids incurring liability (absent negligence or malfeasance). These recommendations

may include ways to maximize the use of informed consent procedures, and potential policy changes that would address disparities in state laws and regulations without waiving research participants' legal rights, while still providing researchers with protection against liability. For example, the purchase of clinical trial insurance with NIH grant funds is permitted for some awards, most commonly to foreign institutions whose countries require such insurance by law. Other potential approaches for mitigating liability or offering incentives have been offered, such as a cap on liability for investigators conducting research on therapeutics used during pregnancy and lactation, providing increased periods of patent exclusivity in exchange for a pregnancy-specific indication in the package label, and additional exclusivity permitted under Title II of the Hatch-Waxman Act (35 U.S.C. §156).

- b. *Systematically pursue a research agenda to inform and enable the use of therapeutics by pregnant women and lactating women:* Issues around liability should not preclude all research from moving ahead, although addressing the issues would help to expand research involving pregnant women and lactating women.

Both government agencies and industry should be involved in assuring that the necessary preclinical data are available in a timely fashion. Appropriate preclinical studies, such as reproductive toxicology studies using animal models, should be conducted for therapeutics still in development with the potential to be used by pregnant women and/or lactating women. Based on data from preclinical studies, decisions about whether to include pregnant women or lactating women in phase III clinical trials should be refocused; the assumption should be inclusion, with a decision on exclusion only if clearly justified by the preclinical data. Currently, however, insufficient time lapses between preclinical studies and the beginning of clinical trials to engage in a separate justification process for inclusion of pregnant women and lactating women. Assuming inclusion would address this issue.

- c. *Identify elements of the VICP applicable to a program of research on therapeutics used by pregnant women and lactating women:* Although no single existing federal program covers all of the issues that need to be addressed, some elements of existing federal programs can serve as models for programs on research on therapeutics for pregnant women and lactating women. For example, VICP retroactively covers clinical research prior to licensing once a vaccine obtains market approval; a similar provision could be considered for this program. HHS and the Department of Justice each have responsibility for a portion of the VICP program.

Any new federal effort should be kept narrowly targeted; for instance, a federal indemnification program could be utilized on a case-by-case basis, such as prioritizing research to focus on on-market therapeutics that are used by pregnant women or lactating women for serious chronic conditions or emergency treatment. The NIH BPCA program similarly prioritizes potential studies on therapeutics for pediatric use. This process takes approximately 1 year to 18 months.



- d. *Determine whether legislation would be required to establish a program of research:* Absent a private sector initiative, policymakers may wish to consider whether federal agencies' existing authority is sufficient for establishing a program to facilitate research and reduce researcher liability (on their own or in partnership with private entities), or whether new authority is required.
- e. *Develop options for funding this program:* The VICP program, which is mandated by law, annually expends the interest on the capital of \$3 to \$4 billion. In fiscal year 2019, this amounted to \$230 million, including awards and attorneys' fees. (Note, however, that the NIH BPCA program is capped by law at only \$25 million/year.)

**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**

The FDA's PLLR, which has been in effect since 2015, is aimed at providing prescribers with relevant information for treating pregnant women and lactating women. Animal data are put in context of human exposure, and human data are added when available. The rule also explicitly requires a statement when no data are available. Over 1,000 drug labels have been successfully converted; however, most drug labels lack human pregnancy and lactation data, indicating significant knowledge gaps.

- a. *Identify the studies needed to obtain clinically relevant data to inform dosing and safety of therapeutics used by pregnant women and lactating women:* For example, PK and PD data are missing for therapeutics used by pregnant and lactating women because these populations have been excluded from most pre-approval clinical testing, and manufacturers are not required to conduct these studies after a drug has been approved. If higher doses are shown to be needed for efficacy, additional safety data also may be required. An NIH-BPCA-like prioritization approach could be used to determine the classes of drugs, conditions experienced by pregnant women and lactating women, and feasibility of studies that would provide dosing and safety data. In establishing such a process, other models, such as the IMI 2 ConcePTION project that includes a discrete component on lactation, may be considered. Establishing a prioritization process could be accomplished within a short timeframe (1 to 2 years). Conducting needed studies would require additional time and resources.

The CDC, in its *Treating for Two* program<sup>22</sup>, uses an approach that focuses on a risk-benefit analysis of drugs that are used by pregnant women who have specific conditions. This approach, which could be emulated more broadly by researchers and funders, should take failure to adequately treat these conditions during pregnancy, which can have detrimental consequences for both the mother and fetus, into account. For women who

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<sup>22</sup> <https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html>

plan to breastfeed, a similar risk-benefit analysis can be established to enable the advantages of breastfeeding for both the woman and the infant.

- 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:* Previous experience has shown that, in some cases, support for additional studies to obtain data for labeling for use by pregnant women and lactating women may not be economically beneficial to manufacturers. Consequently, incentives to industry may encourage additional studies and data sharing. For example, for New Drug Applications/Biologic Licensing Applications or drugs that recently have been approved, incentives such as research tax credits authorized by the Orphan Drug Act may encourage additional testing and data collection. Government-funded programs may require legislative authority and additional funding but are more likely to have formal data-sharing policies in place.<sup>23</sup> However, currently there are no legislative mandates related to the provision of data on pregnant women and lactating women in clinical studies.
- c. *Obtain sufficient data on the use of therapeutics by pregnant women and lactating women:* The FDA does not currently have the authority similar to that for pediatric studies that are mandated by the PREA. Because post-market studies may not be sufficient, and additional on-market drug studies are needed to provide safety and efficacy information for pregnant women and lactating women, government-funded researchers would need the specific authority to conduct this research. Researchers (and funders) who are interested in the underlying conditions experienced by pregnant women and lactating women, even if pregnancy/lactation are not their areas of expertise, could contribute to this work (see Figure 1).
- 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:* Models must be developed that will inform discussions of the whether use of a drug or therapeutic poses additional risk, such as:
- Models of drug concentrations and PKs in pregnant women (second and third trimesters and postpartum)
  - Models of partitioning of drugs or therapeutics into human breastmilk (which are dependent on chemistry and protein binding)
  - Models of drug concentrations (incorporating transplacental transfer) in neonates and infants that consider evolving volume of human breastmilk intake, hepatic and renal clearance
  - The relationship of drug concentration in neonates and infants to clinical effect

For model development, a consortium effort could be considered to leverage available resources. Examples of such consortia or similar initiatives include the Health

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<sup>23</sup> <https://grants.nih.gov/grants/policy/data-sharing>

Environment Sciences Institutes<sup>24</sup> the FDA's Critical Path Initiative<sup>25</sup>, and the IQ Consortium<sup>26</sup>. NIH should review ongoing efforts to coordinate and explore possible collaboration with the IMI 2 ConcePTION project. NIH also has several existing networks, such as the Maternal and Neurodevelopmental Outcomes of in Utero Antiepileptic Drug Exposure network funded by the National Institute of Neurological Disorders and Stroke (NINDS), that support model development.

The development of specific models is estimated to take from 2 to 5 years. In addition, many pharmaceutical companies have model developers on staff and the requisite infrastructure to assist with or lead this effort; a public-private partnership may facilitate model development for drug concentrations and PKs.

Unlike pregnant women, women who are lactating can consent on their own for research participation under any current section of the human subjects regulations, so these proposals primarily apply to augmenting pregnant women's participation in research. However, extremely limited data exist to inform lactating women's decisions whether to participate in research. Consequently, additional studies would benefit this group as well, such as studies of pharmacogenomics in lactating women of ultra-rapid metabolizers that can produce high concentrations of the drug in human breastmilk.

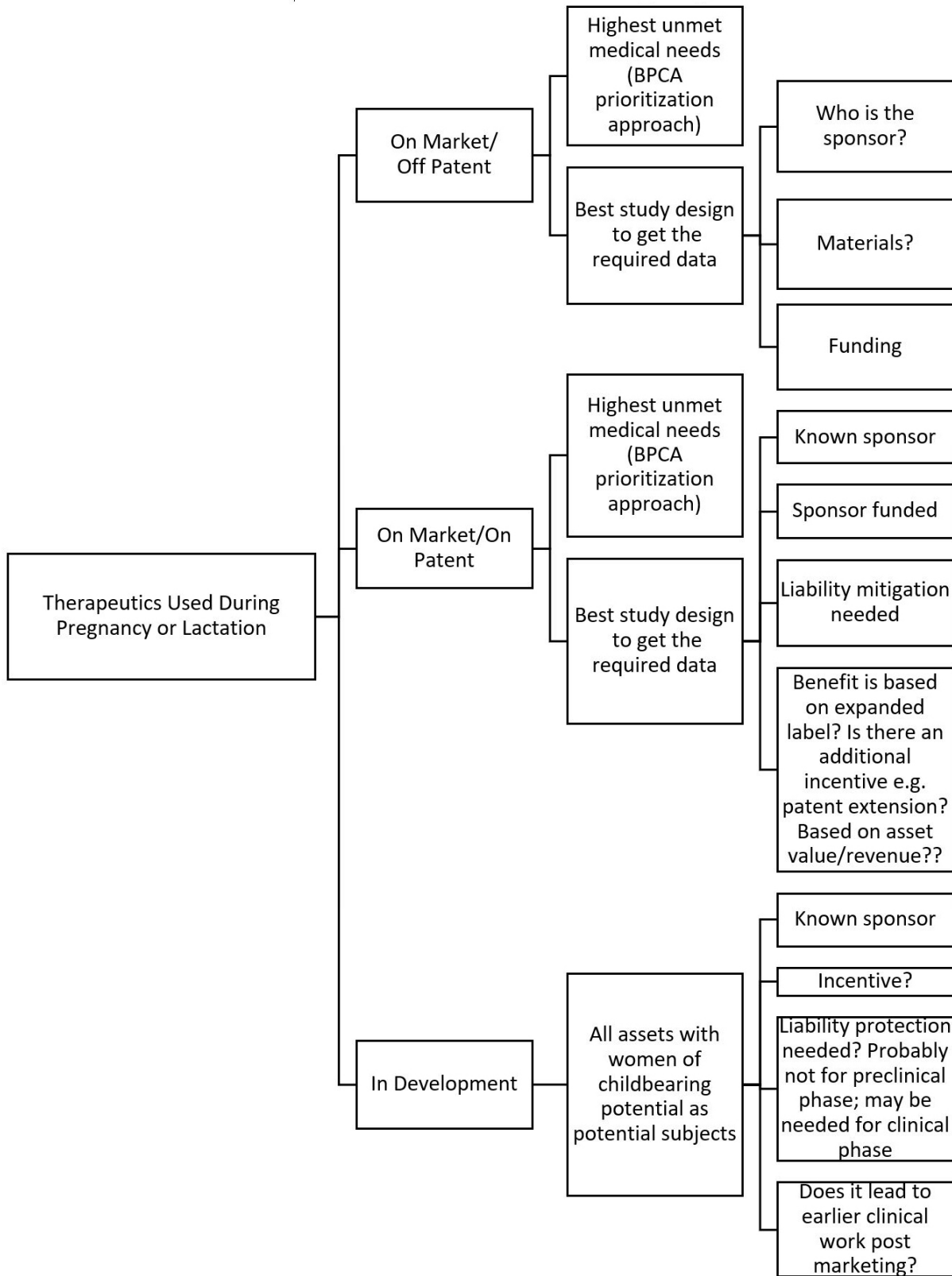
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<sup>24</sup> <https://hesiglobal.org>

<sup>25</sup> <https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative>

<sup>26</sup> <https://iqconsortium.org>

**Figure 1: Liability Considerations for Therapeutics Used During Pregnancy or Lactation**



## PRGLAC Implementation Plan: Recommendation 8

### ***Rec. 8. Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the NIH BPCA as a model***

To date, pregnant women and lactating women have not routinely been included in clinical research. A dedicated infrastructure to address research gaps by studying therapeutic products used off-patent by pregnant women and lactating women is required to ensure that these women and their healthcare providers have sufficient information on dosing, safety, and efficacy. Existing research networks could be utilized to create a research program similar to the NIH portion of the BPCA program.

#### **8A. Provide specific funding**

- a. *Establish infrastructure to carry out testing of drugs commonly used in, or with high impact for, pregnant women and lactating women:* At present, the pharmaceutical industry have no incentives and limited clinical trial and research infrastructure to evaluate products in pregnant women and lactating women once those products are off-patent and/or available as generic products. Any research program to test drugs or other therapeutics in pregnant women and lactating women likely would need public funding, similar to the pediatric drug testing research program established by the NIH to carry out its portion of BPCA. NIH has developed a successful collaboration with the FDA under the BPCA program. Lessons learned in the establishment and management of that program could be applied to facilitating a similar program for testing therapeutics used by pregnant women and lactating women.<sup>27</sup>

A dedicated infrastructure to conduct this research on drugs and biologics used by pregnant women and lactating women would help to provide information on appropriate dosing, safety, and efficacy, which is scarce at present. Testing could be conducted with both on- and off-patent drugs for which there is inadequate information specific to pregnant women and lactating women to provide guidance to women and their healthcare providers for making healthcare decisions. Research should also be conducted on dietary supplements used by pregnant women and lactating women.

Utilization of existing infrastructure and research networks would provide a cost-efficient and expedient approach, but additional funding would be required. For example, the NIH BPCA program already supports the PTN to conduct pediatric drug testing. The PTN also is conducting research on drugs used by lactating women (e.g., the Commonly Used Drugs During Lactation and Infant Exposure [CUDDLE] study). To help coordinate drug testing along the continuum from pregnancy through lactation, the PTN could work with the NIH-funded MFMU Network, leveraging the expertise of CUDDLE researchers and NIH's Obstetric and Pediatric Pharmacology Research Centers (OPRC) Network.

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<sup>27</sup> <https://www.nichd.nih.gov/about/advisory/PRGLAC>: Report to the Secretary, p. 362

Another approach would be to extend ongoing pregnancy studies that are testing therapeutics postpartum so that studying the same drugs used during lactation also would be possible.

- b. Maximize use of existing data:* Existing datasets also can be leveraged to design studies, simulate doses, and clinical trial design that meets regulatory standards. Since many drugs already have been tested in non-pregnant adults, the amount of data needed for initiation of clinical trials specific to pregnant women and lactating women may be minimal. Data may be available through FDA-required pregnancy registries. In addition, incentives (including monetary compensation for time spent) to healthcare providers to enter data into registries could be explored. Streamlining the forms and permitting clinicians to bill payers for this activity would encourage participation. (One possible model is the meaningful use provision of the Affordable Care Act, which provides incentive pay to hospitals and health centers that meet certain EHR criteria.)

Another approach is to support the shared cost efforts of generic manufacturers to join a pregnancy registry to obtain a greater range of data.

- c. Technology Development:* Developing technology that could potentially substitute for or augment human clinical trials could expedite research on therapeutics used by pregnant women or lactating women. Animal models may not always be optimal substitutes for dosing-related information. Developing and validating alternative tools, such as “tissue-on-a-chip” models, for placenta, mammary, liver, and kidney, could provide critical information on drug metabolism during pregnancy and lactation. Physiologically based pharmacokinetic models can inform trial design and dose selection and microphysiological systems approaches also could be leveraged to advance drug testing.

Using current funding levels for these networks as a guide, approximately \$12 million in additional funds would be needed for research related to drug testing in pregnancy, with an additional \$4 million to support lactation-related research. Because the NIH-supported OPRC and MFMU Networks already are in place, a research program similar to the BPCA program could be established within 1 to 3 years, pending available funding. Within 3 to 5 years, new clinical trials in studying therapeutic products used by pregnant women and lactating women could be launched, again, with additional resources.

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

Similar to the lack of pediatric drug testing three decades ago, many drugs and other therapeutics used by pregnant women and lactating women have not been tested specifically for use in these populations. The BPCA legislation was aimed at addressing the lack of pediatric therapeutic development. Included in the NIH portion of the program, which provides testing of largely off-patent drugs, a prioritization process was established to permit testing on the drugs that were most used and needed in children. A similar process, incorporating lessons learned from the BPCA prioritization process, could be developed for pregnant and lactating women.

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

NICHHD leads the trans-NIH portion of the BPCA program, coordinating the research efforts of the NIH ICs that have an interest in pediatrics. In consultation with pediatric experts from the FDA, academia, and industry, NICHHD regularly publishes an updated, prioritized list of drugs or indications that require further investigation due to lack of dosing, safety, or efficacy data. In addition, NIH sponsors clinical trials for drugs on the priority list through its PTN and submits study data to the FDA for consideration of label modification. These data are also made available to researchers and the public through NICHHD's DASH.

As required by law, the NIH BPCA Working Group revisits the priority list approximately every 3 years, following the steps below. Elements of this process could inform the development of a similar process for prioritizing drugs for pregnant women and lactating women:

- *Request for nominations:* published in the *Federal Register*
- *Nominations/stakeholder input review:* Threshold criteria to be met include whether the area/need is relevant to the mission and goals of the BPCA program, and assurances that there are no disqualifying ethical concerns. Nominations meeting those criteria are scored on the following:
  - o Evidence Feasibility
  - o Urgency
  - o Population
  - o Impact
- *Finalized List of Priority Needs in Pediatric Therapeutics:* also published in the *Federal Register* (see <https://www.nichd.nih.gov/sites/default/files/inline-files/2018PriorityList-Feb19.pdf> as one example)

- b. *Establish separate prioritization processes and programs for testing therapies and/or conditions in pregnant women and lactating women:*

This effort could dovetail with the strategies currently under consideration to address and reduce maternal mortality and severe maternal morbidity. Acquiring evidence to improve dosing information on pharmaceuticals and therapeutics used by pregnant women and lactating women, and the development of safe and effective novel therapies may augment these efforts. An initial decision is whether these priority listings should combine therapeutic testing for both pregnant women and lactating women, or whether separate but linked listings should be developed. Additional priorities should include pharmaceuticals used to treat conditions related to pregnancy, and those that can be used to treat low milk supply.

Many of the same agency stakeholders, including NIH, FDA, academic researchers, industry, women's health organizations, and professional societies, involved in the BPCA pediatric drug testing programs should also participate in a similar effort for testing therapeutics used by pregnant women and lactating women. One agency could take the lead to establish and maintain these prioritization processes for prioritizing studies on therapeutics used during pregnancy and lactation but produce separate work products for therapeutics used during pregnancy and those used during lactation. Policymakers who have shown an interest in PRGLAC's work should be kept apprised about new developments.

Within 1 to 3 years, a separate prioritization process for therapeutics used by pregnant women and lactating women could be established, with programs to implement testing established within 3 to 5 years, pending available funding.



## **PRGLAC Implementation Plan: Recommendation 9**

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

The 2018 PRGLAC Report documents two major issues facing pregnant and lactating women and their healthcare providers. First, the report highlights how little evidence-based information currently is available to inform safety and appropriate dosing of the therapeutics women are already using to treat underlying medical conditions, as well as new or better therapeutics aimed at treating pregnancy- or lactation-related conditions.

Second, the report suggests that, absent major incentives (and mitigation of disincentives, such as liability concerns) for pharmaceutical companies to support discovery of new molecular entities for drugs used by pregnant or lactating women, government-supported programs may be best placed to galvanize research in this area. The steps to implement Recommendation 9 focus on conditions specific to pregnancy and lactation; the other Task Force recommendations address obtaining information on therapeutics for all conditions that pregnant or lactating women may have.

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

- **Unmet need examples in lactation: low milk supply, mastitis**
- **Unmet need examples in pregnancy: preterm labor, hyperemesis**

Although a number of federal agencies, academic institutions, and industry are conducting or supporting research on drugs and therapeutics used by pregnant women and lactating women, none of these is creating an overarching prioritization process for studies on these therapeutics or to fill therapeutic gaps related to conditions specific to pregnant women and lactating women. Given the relative dearth of research in these areas, a systematic prioritization process would ensure that the most pressing public health needs are addressed by researchers and funding agencies in deciding which studies to pursue first. Some of the federal agencies involved in PRGLAC could lead these prioritization efforts under their existing authorities.

- a. *Identify a process for prioritizing the development and manufacture of new drugs and therapeutics for conditions arising during pregnancy and lactation:* To create a separate prioritization process for studying therapeutics used, or that could be used, by pregnant women and lactating women, one possible approach could include the following steps:
  - Identify a lead agency to coordinate separate prioritization processes for identifying therapeutic gaps in diseases, disorders, or conditions specific to pregnant women and to lactating women for which more complete knowledge of drugs and biologics are needed. In implementing development of a process to identify research gaps for therapeutics prescribed to children under the BPCA, the NIH has the experience to develop such a process (see also Recommendation 8B).

- The lead agency would publish a request for nominations of: 1) research needs, (e.g., the development of drugs/therapeutics for conditions experienced specifically by pregnant or by lactating women that do not have adequate treatment options), with pregnancy-specific conditions separated from lactation-specific conditions (e.g., perinatal mood disorders or hyperemesis versus low milk supply or mastitis); and 2) drugs/therapeutics used to treat medical conditions in pregnant women and lactating women but that do not have adequate dosing, safety, or efficacy data.
- Disseminate the request for nominations widely by publishing on the NIH website and in the *Federal Register*, and through outreach efforts to other agencies involved in PRGLAC (e.g., FDA, CDC, HRSA, AHRQ, VA and others), professional societies and research organizations, and women's health and other stakeholder groups.
- Review nominations using criteria that include available evidence (unmet need or gaps in information), feasibility (prevalence, expertise), urgency (immediacy of obstetrical or lactation needs for a therapeutic), and impact (severity of condition, cost, frequency of use, availability of alternative treatments). Consider focusing on therapeutics related to prevention or treatment of a critical health or societal burden. Other prioritization lists, such as that maintained by the World Health Organization (WHO), should also be consulted to prevent unnecessary duplication.
- Finalize and publish prioritized lists of therapeutic research needs for pregnant women and lactating women. Establishing these priority listings could take about 12 to 18 months.

**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**

- 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:* No single governmental model exists that would foster the development of therapeutics for pregnant and lactating women, especially for conditions that arise because of pregnancy or lactation. However, to mitigate issues of liability and identify incentives for research, this program could incorporate elements of existing, successful federal programs, such as the following:
  - The NIH Vaccine Research Center functions as a public analogue of a private sector biotechnology company that encompasses basic, translational, and clinical research/trials under one multidisciplinary umbrella, along with the necessary infrastructure to support these activities. The purpose of this intramural program is to accelerate the process of scientific discovery leading to the design and development of drugs and biologics.
  - BARDA provides incentives to investigators/sponsors to progress testing of therapeutics from phase I to phase II.

- b. *Provide incentives to industry for research on therapeutics to treat conditions specific to pregnant women or lactating women:* The FDA's Rare Pediatric Disease Priority Review Voucher Program (priority review vouchers for future use or sale awarded to companies that receive approval for certain applications for treatment of rare pediatric diseases or conditions) offers one model. Another incentive program, under the Orphan Drug Act, allows a drug or biologic product that is intended for treatment of a rare disease or condition to receive orphan exclusivity and a special designation. This program also provides tax credits for qualified clinical testing of these drugs. Additional considerations could include innovative incentives directed specifically to an original application for a pregnancy- or lactation-specific condition that has been identified on the prioritization list. A meeting of large and small pharmaceutical company representatives could be convened to generate novel ideas (see also Recommendation 7A).
- BPCA provides legislative authority to provide additional marketing exclusivity to manufacturers that conduct studies of drugs being prescribed to children.
  - The VICP, administered by HRSA provides a no-fault alternative to the traditional legal system for vaccine injury petitions (licensed vaccines only). The program's authority was specifically amended in 2016 to include pregnant women and their offspring.
- c. *Establish the infrastructure needed for this new program:* Establishing a federally supported program aimed at developing and testing therapeutics intended to treat conditions specific to pregnant women and lactating women that incorporates elements of other successful federal programs would require both new authority and additional resources. Additional considerations include working with IRBs and ethics committees, which play important roles in reviewing proposed research, to facilitate research with pregnant women and lactating women (see Recommendation 4).

## PRGLAC Implementation Plan: Recommendation 10

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

In January 2017, HHS and other agencies that adopted the so-called “Common Rule” regulations for the protection of human subjects in research issued a final rule to revise and update regulations at 45 CFR 46, Subpart A. These revisions were implemented in January 2019. Among the changes was the removal of pregnant women as an explicit example of a “vulnerable population” requiring additional ethical scrutiny prior to participating in research. The FDA is currently working to harmonize its regulations with the Common Rule to the extent practicable and consistent with other statutory provisions (see Recommendation 1).

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

##### *a. Both investigators and sponsors:*

Exclusion of pregnant women or lactating women should be justified in clinical studies conducted in females of reproductive potential. Absent a clear justification for exclusion of pregnant women or lactating women (e.g., ethical or safety concern), enrollment of pregnant or lactating women in clinical studies should be considered.

##### *b. Sponsors (i.e., drug developers)<sup>28</sup>:*

Authorize the FDA to require drug developers to provide a “PRGLAC Study Plan” and “PRGLAC Assessment” during drug development to ensure that pregnant and lactating women are included in drug development plans, and that any exclusion of pregnant women or lactating women from drug development plans is justified. This requirement would potentially be limited to drugs and biological products under development that would likely be used in females of reproductive potential. A PRGLAC Study Plan would outline the data that are already available, the need for additional data, and if so, the data that will be collected as part of the overall drug development program. Such information could include but is not limited to pharmacokinetic (PK), pharmacodynamic (PD), pharmacogenomic, safety and efficacy data of the drug or biologic in pregnant women and lactating women. However, when additional data may be needed, not all types of data would always be needed, and in many cases, additional PK and safety data may be sufficient. A PRGLAC Assessment could include data collected as described and agreed upon in the PRGLAC Study Plan and would provide information to support appropriate labeling of products when used during pregnancy and/or lactation. If data as described above are not available for pregnant women or lactating women and cannot for ethical or safety reasons be gathered from these groups, the PRGLAC Assessment should state why data cannot be obtained. Since this new requirement would involve additional

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<sup>28</sup> Drs. Bucci-Rechtweg and Ternik did not concur with implementation step 10A(b).

infrastructure requirements for drug developers and FDA, a timetable for implementation that includes input from stakeholders should be considered.

- 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”:*<sup>29</sup> The FDA could lead a process involving relevant stakeholders to determine such criteria. Among criteria to consider:
- The drug or biologic product would not meet one of the prioritized needs as identified through a formal prioritization process (see Recommendations 8B and 9A)
  - The necessary studies are shown to be impossible or highly impracticable for reasons such as, the condition does not exist in pregnant women, or the drug is not approved for use in females of reproductive potential.
  - Available evidence strongly suggests that the drug or biological product would be ineffective or unsafe in pregnant women and/or lactating women
- 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:*<sup>30</sup> These criteria would permit the FDA to grant a full or partial waiver, either on its own initiative or by written request of the sponsor. The criteria should clarify the circumstances (e.g., insufficient data or time permitted) under which a deferral may be granted. The FDA could lead a process to determine the criteria. Among criteria to consider:
- The drug or biologic product would not meet one of the prioritized needs as identified through a formal prioritization process (see Recommendations 8B and 9A)
  - The necessary studies are shown to be impossible or highly impracticable
  - Available evidence strongly suggests that the drug or biological product would be ineffective or unsafe in pregnant women and/or lactating women
- e. *Exclusion of pregnant women or lactating women from clinical research should be justified in investigational new drug applications for new drugs/indications or biological products:*<sup>31</sup> Instead of justifying inclusion of pregnant women or lactating women in clinical research, investigational new drug applications (INDs) for new drugs or biological products (including a proposed study for a new indication to an already approved drug or licensed biological product) should now include justification for excluding these groups. IRBs (see Recommendation 10D) and the FDA will review study designs with inclusion as the default, pending available PK/PD data.

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<sup>29</sup> Drs. Bucci-Rechtweg and Ternik did not concur with implementation step 10A(c)

<sup>30</sup> Drs. Bucci-Rechtweg and Ternik did not concur with implementation step 10A(d)

<sup>31</sup> Drs. Bucci-Rechtweg and Ternik did not concur with implementation step 10A(e)

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

Extensive physiological changes associated with pregnancy, which themselves may differ depending on the age of the woman, may alter drug PK which may affect the safety and efficacy of a drug administered to a pregnant woman through alterations in drug absorption, distribution, metabolism, and excretion. The goal is to obtain enough PK/PD information to determine the dosages needed for efficacy and/or safety at different stages of pregnancy and lactation.

- a. *Encourage investigators to follow FDA guidance about trial design and inclusion of pregnant and lactating women in clinical research:* In 2018, the FDA published a draft guidance on the inclusion of pregnant women in clinical trials.<sup>32</sup> For example, the guidance states that because of the extensive physiological changes associated with pregnancy, PK parameters may change, sometimes enough to justify changes in dose or dosing regimen. This document also provides guidance concerning women who become pregnant while on an investigational drug (see Recommendation 10E).

The FDA also has issued guidance on adaptive designs for clinical trials of drugs and biologics,<sup>33</sup> which provides information on managing Bayesian and adaptive complex designs. Additional pertinent FDA guidances provide useful information to investigators considering research on drugs or biologic products that may be used by pregnant women or lactating women.<sup>34</sup> While these documents do not establish legally enforceable responsibilities on the part of investigators/sponsors, they may provide investigators with methods of including pregnant women and lactating women in clinical research.

In addition, professional societies, such as ACOG, also have published recommendations on the Ethical Considerations for Including Women as Research Participants.<sup>35</sup>

- b. *Prioritize the development of new models for testing the effects of drugs/biologic products:* New models are being developed that may especially prove useful for testing the effects of drugs on human tissue (“tissue-on-a-chip,” placental models, or *in silico* testing, which involves virtual investigations using computer modeling) to better gauge

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<sup>32</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnant-women-scientific-and-ethical-considerations-inclusion-clinical-trials>. When finalized, this guidance will reflect FDA’s current thinking on this issue.

<sup>33</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry>

<sup>34</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-pregnancy-study-design-data-analysis-and-impact-dosing-and-labeling>; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnancy-lactation-and-reproductive-potential-labeling-human-prescription-drug-and-biological>; and <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design>

<sup>35</sup> <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2015/11/ethical-considerations-for-including-women-as-research-participants>

their potential effects on research participants and predict potential toxicology.<sup>36,37</sup> As these new models are being developed, particular attention should be paid to creating models that help move research from pre-clinical to clinical testing, such as the use of real world data to support other preclinical information (see also Recommendation 2). The acceptability of any new model must be reviewed and agreed upon with FDA if intended to support regulatory decision making.

**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**

- 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:* Studies that result in data on the PKs, PDs, pharmacogenomics, safety, or efficacy of drugs used by pregnant women or lactating women should be made available to the research community through a public resource, such as NICHD’s DASH.<sup>38</sup> While drugs currently on the market have rarely been tested for use by pregnant women and lactating women, these studies may provide data useful for studies on investigational drugs intended to treat similar conditions in non-pregnant women.
- b. *Support additional publicly funded research aimed at filling research gaps:* Funding agencies should conduct and support basic research on disease mechanisms and potential drug targets for disorders specific to pregnancy and lactation, and conditions known to occur in pregnant women and lactating women. Agencies also should support and conduct PK, PD, pharmacogenomic, dosing, and safety studies of drugs and biologics for use during pregnancy and lactation.
- c. *Authorize the FDA to require drug developers that are submitting new drug/biologics license applications to provide a “PRGLAC Assessment” and “PRGLAC Study Plan” (see Recommendation 10A).*<sup>39</sup>

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

- 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:* Lack of guidance<sup>40</sup> in this area was identified as a barrier to inclusion of these groups in clinical research. The HHS OHRP would need to lead this effort, with input

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<sup>36</sup> <https://www.sciencedirect.com/science/article/pii/S0003267018308031>

<sup>37</sup> <https://www.vanderbilt.edu/vprompt/>

<sup>38</sup> <https://dash.nichd.nih.gov>

<sup>39</sup> Drs. Bucci-Rechtweg and Ternik did not concur with implementation step 10C(c)

<sup>40</sup> Note: as used here, PRGLAC is referring to generic guidance, not FDA-published guidances or federal regulations.

from professional societies, women’s health organizations, and other members of the public.

- b. *Standardize the informed consent procedures for enrolling pregnant women and lactating women in clinical research:* These standard procedures would include template consent forms and guidelines for counseling potential enrollees about the interventions to be tested, such as assessments of pharmacokinetics or safety and effectiveness of a drug or biologic. Although uniform consent procedures would not mitigate liability concerns altogether, such procedures could serve as a useful baseline for IRB decision making.
- c. *Provide IRBs with recommended practices to facilitate inclusion of pregnant women and lactating women in study designs:* To assist IRBs with their ethics analyses of proposed studies, practices to facilitate inclusion of pregnant women and lactating women in clinical research, while ensuring appropriate protections could include the following elements:
  - Routinely include experts in obstetrics, maternal-fetal medicine, and pharmacology in IRB membership
  - Provide updated information on revised Common Rule regulations that remove pregnant women as an example of a vulnerable population
  - Enlarge understanding of traditional ethical principles in support of requiring justification of exclusion of pregnant women or lactating women in studies under consideration
  - Consider additional safety monitoring to ensure continued protection

HHS could provide guidance to IRBs that outlines and explains these practices in the *Federal Register*.<sup>41</sup>

**10E. Develop a systematic plan for if a woman becomes pregnant in a study to include whether product should continue<sup>42</sup>, if un-blinding is necessary, how to capture opportunistic information on pharmacology, clinical data, and pregnancy outcome information**

- a. *Encourage investigators to follow FDA guidance about trial design and inclusion of pregnant and lactating women in clinical research:* The 2018 FDA Draft Guidance<sup>43</sup> (see Recommendation 10B) provides recommendations about steps to be taken when a study participant becomes pregnant during a clinical trial. For example, the guidance

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<sup>41</sup> <https://www.federalregister.gov/documents/2018/05/17/2018-10441/institutional-review-board-written-procedures-guidance-for-institutions-and-institutional-review>

<sup>42</sup> PRGLAC notes clarification here, that this means whether the product being tested should continue to be used by the pregnant woman participating in the study.

<sup>43</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnant-women-scientific-and-ethical-considerations-inclusion-clinical-trials>. When finalized, this guidance will reflect FDA’s current thinking on this issue



states that “*unblinding should occur so that counseling may be offered based on whether the fetus has been exposed to the investigational drug, placebo, or control. The risks and benefits of continuing versus stopping investigational treatment can be reviewed with the pregnant woman. Pregnant women who choose to continue in the clinical trial should undergo a second informed consent process that reflects these additional risk-benefit considerations.*” After review of the risks and benefits of continuing the trial, those women who continue to participate should be provided a second informed consent process.<sup>44</sup> The Task Force recommends that a standardized re-consent template should be developed and disseminated.

- b. *In any of these scenarios, collect and report the data on pregnancy outcomes:* NIH and other agencies that fund research could establish a policy that encourages grantees to capture and report opportunistic data should participants in their clinical studies become pregnant.

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<sup>44</sup> Briggs GG et al. Should pregnant women be included in phase IV clinical drug trials? *Am J Obstet Gynecol* 2015; 213: 810-5.

## **PRGLAC Implementation Plan: Recommendation 11**

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

Multiple stakeholders are supportive of expanding research on therapeutics used by pregnant women and lactating women, including a wide range of governmental and non-governmental entities, such as academic and industry researchers, professional societies, and nonprofit organizations involved in pregnancy and lactation research. NIH, FDA, and other U.S. agencies should continue to reach out to international regulatory and research entities, such as the IMI 2 ConcePTION Initiative and the WHO, to learn from their experiences and explore data sharing. Moreover, the development of a more streamlined process for collaborations and public-private partnerships among industry, philanthropy, and government—such as those occurring with multiple stakeholders to address the SARS-CoV-2 pandemic—for research on therapeutics used by pregnant women and lactating women could efficiently combine and maximize the expertise of these partners.

Clinical research networks could be ideal for supporting research on pharmaceuticals and therapeutics prescribed for pregnant women and lactating women. They often have stable infrastructure over time, can conduct multiple studies simultaneously, and are able to oversee the long-term monitoring often required by regulatory bodies. Current research networks (see Appendix 2), including federally funded networks, could be expanded or more fully utilized to conduct studies on therapeutics used by pregnant women and lactating women. One avenue for increasing their reach would be to leverage these networks by enabling non-network researchers to access network data and cohorts to perform pharmacologic studies. In addition to specific funding opportunities, improving the use and usability of registries and other databases that include data on pregnant women and lactating women so that researchers interested in this area can conduct new analyses, adding to our knowledge base, would provide another incentive. Further, a trans-NIH coordinating committee could facilitate the exchange of knowledge and expertise among extramural grantees who are newer to the field and those who are experienced in pharmacology and specific conditions that affect pregnant women and lactating women.

Utilizing existing research networks for clinical trials, or expanding current case-control studies (comparing treatments for conditions in women who are pregnant or lactating to untreated pregnant women or lactating women), to evaluate therapeutics used by pregnant women and lactating women could begin within 1 to 2 years, pending available funding. Obtaining detailed and updated information on current pregnancy and lactation studies would be a prerequisite to beginning any new efforts.

**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**

- a. *Expansion of current networks:* Current research networks that are deemed by their funders to be successful (see Appendix 2) could be expanded to conduct studies on therapeutics used by pregnant women and lactating women, pending available funding. These networks conduct large clinical trials that address conditions leading to maternal mortality and severe morbidity. With additional resources, these infrastructures can efficiently be leveraged to perform pharmacologic research more cost-effectively than building a new infrastructure. Adequate support for existing infrastructure and adding sites to increase diversity among participants (including representation from racial and ethnic minority groups, rural, tribal, and other underserved communities) would ensure that research findings apply to most pregnant women and lactating women and allow for longer-term follow up of pregnant women and lactating women, and their offspring. While federal funding often provides the base for research infrastructure such as a network, collaborations with philanthropic and other sources of support can extend a network's efforts.

One challenge for research networks relates to protected time and mentorship, particularly for newer researchers since most clinical researchers in this field are also clinicians. For example, for participation and data reporting on for trials on certain conditions, CMS gives credit to clinicians in the Merit-based Incentive Payment System. Because some grant mechanisms demand significant time spent on research, this may discourage young researchers from entering the field. A review of these mechanisms and creation of incentives to optimize participation for clinician-scientists may be helpful.

- b. *Conduct additional research on therapeutics used by pregnant and lactating women in currently available research networks:* Through new funding opportunities, pending available funding, NIH could encourage investigator-initiated projects in this area to be conducted within an appropriate network such as, but not limited to, the NICHD-funded MFMU or OPRC Networks, both of which have already conducted numerous studies to test agents used in these populations. Researchers who are not currently part of the networks could be provided access to its expertise and infrastructure to ensure the high level of safety and standardization necessary to conduct this type of clinical trial. Other federal agencies, such as the VA, have practice-based research networks that could facilitate the testing of women's health-related interventions, including those related to pregnancy and birth.
- c. *Create a new network model specifically for the testing of therapeutics used by pregnant and lactating women:* One model to consider is the NICHD-funded PTN that allows participating sites across the country to cooperate in the design and conduct of trials to provide evidence for optimal dosing of medications prescribed, but not labeled for,

infants and children. Similar research focused on therapeutics used during pregnancy and lactation would benefit from the establishment of a similar network, with the goals of:

- Embedding experts (e.g., pharmacometricians, biostatisticians, pharmacologists, pharmacoepidemiologists) versed in study design and statistical methods for studies where subgroups of populations may be limited
- Conducting research using innovative study designs, such as an adaptive clinical trial that would allow the protocol to be conducted at different sites, each focusing on one outcome, and then aggregating the results; or, opportunistic sampling models that collect samples from pregnant women and lactating women who are already using the pharmaceuticals
- Performing physiologically based pharmacokinetic (PBPK) modeling to better inform trial design and/or dose selection for pregnant and lactating populations
- Developing protocols to test and analyze potential standards of care to identify the best standard to be utilized in both clinical care and future trial design
- Identifying and testing specific clinical outcome measures and biomarkers relevant to conditions that preclude pregnant women or lactating women from using therapies that are routinely prescribed for conditions in non-pregnant, non-lactating women

*d. Develop streamlined processes for collaborations among industry, philanthropy, and government to support clinical research:* Facilitating agreements among these entities that would permit multiple study collaborations would allow research to move ahead more efficiently than the current single agreement per single study approach. One novel partnership that could serve as a model is the IMI 2 ConcePTION initiative, which is funded equally by industry and the European Union to conduct health-related research and innovation; currently, the partnership is funding 144 projects. A similar approach in the United States could facilitate testing of therapeutics used by pregnant women and lactating women and encourage industry participation. For example, collaborations could support opportunistic PK studies to build PBPK models, which can then be used to better understand dosing in pregnancy or lactation in current drugs as well as future drug development. Such models could increase the availability of data to support dosing and safety information on new drugs prior to their approval. In addition, the use of modeling and simulation to leverage existing data and develop protocols, endpoints, and biomarkers can be used and applied during therapeutics development, with the goal of increasing drugs used to treat pregnancy-related conditions.

NIH could explore public-private agreements involving parties from different sectors, working through the FNIH. This approach also would ensure that findings from the research collaboration would be published and widely available.

*e. Review and address the ability of pregnancy registries to maximize enrollment and make data available for research:* Voluntary registries of provider-entered data on medications

used by pregnant women and lactating women have led to incomplete datasets. Clinicians are often unaware of registries or cannot afford the staff time to enroll their patients. In addition to compensating clinical staff for data entry, another approach would be to allow pharmaceutical company representatives to provide FDA-reviewed materials on product-specific registries during prescriber/clinician visits. Researchers could also collaborate directly with EHR companies and data warehouse companies to add people to their clinical registries by pulling data from the EHRs to identify people eligible for research studies. App/smart phone technologies for direct engagement with pregnant women and lactating women, such as the NICHD-funded PregSource<sup>®</sup> research registry, allows women to provide their deidentified data directly to NIH for research purposes. Pilot studies that encourage the use of standardized data and testing these approaches would help to address the barriers to recruitment and explore strategies for sharing data.

- f. *Facilitate comparative effectiveness trials, trials embedded within clinical care (“pragmatic trials”), and case-control studies:* Agencies and organizations that implement the PRGLAC recommendations could work with CMS to encourage healthcare providers working in managed care organizations to enroll their patients in comparative effectiveness research studies, potentially through PCORI. CMS could also help facilitate access to data for analysis. These data can also be used to design comparative-effectiveness and cluster-randomized trials by providing eligibility or outcomes data, in a manner similar to how Medicare data is used in some cancer studies. Federal agencies involved in these types of research, such as NIH, FDA, and CMS, could consider meeting with PCORI to explore strategies for improving research in a diverse group of pregnant women and lactating women, such as incentivizing health centers receiving CMS funds to conduct research or provide data (the model used to ensure that hospitals initiated EHR systems).

In addition to regular interactions among NIH, FDA, and other U.S. agencies and international regulatory and research entities, a trans-NIH coordinating committee or similar structure might help facilitate the exchange of expertise and mentoring between established researchers who may be new to the field and those who have specific knowledge of pharmacology or conditions that affect pregnant women and lactating women.

Utilizing existing research networks for clinical trials, or expanding current case-control studies, to test therapeutics used by pregnant women and lactating women could begin within 1 to 2 years, pending available funding. Obtaining detailed and updated information on current pregnancy and lactation studies would be a prerequisite to beginning any new efforts. Issuing FOAs and funding new studies, scaling up additional infrastructure, and developing new partnerships and collaborations would likely take between 2 and 4 years. Within 3 to 5 years, should these systems and resources be put into place, the ability to conduct new studies efficiently would increase. An estimated \$40 million/year in additional funding for research networks and infrastructure would support approximately five Phase III trials per year; \$10 million/year for early phase pharmacology studies would galvanize the research community

into engaging in these types of studies. With \$11 to \$12 million a year, model entities such as the PTN can execute one or two large PK studies annually; some studies evaluate multiple drugs and use opportunistic study designs.

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

- a. *Provide additional resources to existing networks (see Appendix 2):* Pending the identification of available funding for new research infrastructure, established networks could receive support for conducting additional clinical research focused on therapeutics used by pregnant women and lactating women. They could also be encouraged, through specific FOAs, to add pharmacology-related expertise to their research teams for additional research with pregnant women and lactating women.
- b. *Establishing standards for assessing risk in pregnancy and lactation research:* NIH, FDA, industry, and other stakeholders could convene a scientific workshop to establish standards for assessing risk in pregnancy and lactation research, appropriate endpoints and identifying factors (e.g., drug-related or condition-related), including those to be used for long-term follow-up of infants (see Recommendation 2). Current challenges for discussion could include identification of “signals” in reproduction/toxicology studies, developing a business case around the risk of studying drugs earlier in pregnancy versus the risks of reducing access to a wider population, and providing sufficient incentives for industry participation.
- c. *Establishing relationships with industry to partner on testing of therapeutics used by pregnant and lactating women:* In addition to the work on standards (see Recommendation 11Bb), NIH, FDA, and other stakeholders, including industry, could work on topics of mutual interest to further research on therapeutics used by pregnant women and lactating women. Examples include agreeing on the parameters of reproductive/toxicity studies, such as the weight of evidence for reproductive or teratogenic risk required, data standards, and developing a business case around the risk of studying drugs earlier in pregnant women. (A model for this effort is the forum convened by the WHO with industry on HIV drugs.)

### **11C. Encourage networks/collaborations to engage in public-private partnerships to facilitate research**

Public-private partnerships need to be developed carefully, with clear objectives established openly by each party, as their interests may not be identical. For example, industry may want product evaluation, foundations may want to meet their missions, clinician-scientists may want to treat their patients, and regulators may want sufficient dosing, safety, and efficacy data. Clearly defining roles and responsibilities and addressing issues such as data sharing, liability, shared costs, and operating procedures must occur before research can begin. The ultimate goal is the establishment of a sustainable organization that can add to current knowledge related to obstetric and lactation pharmacology.

Several models already exist for successful collaborations, including an industry partner working with a publicly funded research network (under a formal agreement), or a foundation sponsoring studies through research networks under the auspices of the FNIH. Establishing a partnership among NIH, FDA, and other U.S. agencies and international regulatory and research entities, such as the European Medicines Agency, the IMI 2 ConcePTION initiative, and the WHO, while involving considerable time and effort, might provide a major increase in our knowledge base about therapeutics used by pregnant women and lactating women.

## PRGLAC Implementation Plan: Recommendation 12

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

In evaluating the safety and effectiveness of drugs and biologics used during pregnancy and lactation, analyses of datasets that link maternal and infant data would minimize biases that may be inherent in using only one dataset alone. For example, Vital Statistics Patient Discharge Data are more complete than using data from birth certificates or discharge data alone. Nonetheless, efforts to link mother-infant data are underway, which should be evaluated and maximized before developing a centralized, harmonized mother-infant linked data system.

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

- a. Establish an ongoing working group within HHS with data and health records expertise:* This group may include federal and non-governmental experts familiar with health systems and data collection, developing platforms for electronic health records and organizations that use those records (e.g., CMS, VA, DoD, CDC, the PCORI Trust Fund,<sup>45</sup> private health insurers, and other payers), as well as individuals with clinical obstetric, pediatric, and pharmacologic expertise. The group can convene workshops, as appropriate, to gather additional expert input.
- b. Review pertinent existing resources and registries:* Beginning with the list compiled for the 2018 PRGLAC Report,<sup>46</sup> the working group should catalogue and study existing systems and registries, both in the United States and in other countries, where EHR usage has been nearly universally adopted to assess the level of success of mother-infant record linkage (as in Australia, New Zealand, and IMI 2 ConcePTION). As part of this review, consider whether any of these established data resources already track, or could be modified to track, lactation. Examples of some existing compilations, databases, and registries to consider include:
  - Pregnancy exposure registries that were designed to collect and evaluate the safety of drugs or biologics identified through NIH's clinicaltrials.gov website<sup>47</sup> or the FDA's Office of Women's Health website<sup>48</sup>
  - The FDA Sentinel system that monitors the safety of FDA-regulated medical products (and is currently being expanded to include mother-infant linkages)<sup>49</sup>

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<sup>45</sup> <https://aspe.hhs.gov/patient-centered-outcomes-research-trust-fund>

<sup>46</sup> <https://www.nichd.nih.gov/about/advisory/PRGLAC> (p. 313 et seq.)

<sup>47</sup> <https://clinicaltrials.gov/>

<sup>48</sup> <https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries>

<sup>49</sup> <https://www.fda.gov/safety/fdas-sentinel-initiative>



- AHRQ's State Inpatient Databases, part of the Healthcare Cost and Utilization Project,<sup>50</sup> a federal-state-industry partnership in health data
  - The DoD Birth and Infant Health Registry<sup>51</sup>
  - CDC Perinatal Quality Collaboratives<sup>52</sup>
  - HealthIT.gov website,<sup>53</sup> which includes information on commonly used data in EHRs
- c. *Develop variables and standard protocols for optimal linkages of mother-infant records:* The working group should review the variables used in existing systems to link mother and infant records, including postpartum data on women, and develop an optimal set of variables to make publicly available and move toward consistent usage. In addition, the group should develop a model for universal standard protocols for linking databases, based on existing data and experiences from state and regional perinatal data from billing records and birth certificates. Ultimately, the goal is to harmonize methods for mother-infant EHR linkage, while complying with federal law, such as the Health Information Technology for Economic and Clinical Health Act and Health Insurance Portability and Accountability Act (HIPAA).

## **12B. Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries**

- a. *Explore hybrid and non-governmental efforts that track pregnancy outcomes data:* Healthcare delivery systems that use EHRs, EHR vendors, hospitals, and professional organizations may provide novel medical data sources; examples include but are not limited to:
- PCORNet<sup>54</sup>
  - Kaiser Permanente/Optum
  - ACOG, which provides information by state on quality collaboratives

Partnerships could be established with these organizations to allow the extraction of chart data for secondary analysis.

## **12C. Use novel data resources**

- a. *Support large post-marketing observational studies to evaluate the safety and effectiveness of medication classes during pregnancy and lactation:* Such studies would serve a critical purpose in the absence of clinical trial data but may be costly.

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<sup>50</sup> <https://www.hcup-us.ahrq.gov>

<sup>51</sup> <https://www.med.navy.mil/sites/nmrc/nhrc/news/pages/news-details.aspx?newsid=72>

<sup>52</sup> <https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pqc.htm>

<sup>53</sup> <https://www.healthit.gov/faq/what-information-does-electronic-health-record-ehr-contain>

<sup>54</sup> <https://pcornet.org/data-driven-common-model>

- b. *Support studies across multiple drugs using the same infrastructure to conserve resources*

Partnerships should be sought to help with both approaches.

## **12D. Use innovative methods of data analytics**

- a. *Identify relevant, innovative methods of data analytics:* Examples of these methods include probabilistic matching, unique identifiers, and natural language processing. Consult experts in academic institutions and associations focused on data analytics, such as:

- American Medical Informatics Association<sup>55</sup>
- American Statistical Association<sup>56</sup>
- CMS<sup>57</sup>

- b. *Use methods of data analytics to link multiple data sources:*

Several federal efforts are maximizing the use of “big data” (aggregating and sharing research datasets to provide sufficient power to answer complex biological questions) to move science forward more quickly. For example:

- The NIH Common Fund program, Big Data to Knowledge, supports the research and development of innovative and transformative approaches and tools to accelerate the utility of big data and data science in biomedical research.<sup>58</sup>
  - CDC’s Childhood Obesity Data Initiative leverages existing information technology tools to facilitate access to individual level, linked, longitudinal data. Data types may include demographics, clinical, and census information such as neighborhood socioeconomics. The information captured includes clinical health outcomes, results from a child’s participation in a clinical or community intervention, and individual and community risk factors.
- 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:* The HHS working group described in Recommendation 12A, or an HHS division such as CMS or the National Coordinator for Health Information Technology, could establish a partnership with organizations focused on data analytics to develop

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<sup>55</sup> <https://www.amia.org>

<sup>56</sup> <https://www.amstat.org>

<sup>57</sup> <https://www.cms.gov/newsroom/data>

<sup>58</sup> <https://commonfund.nih.gov/bd2k> ; see also NIH Strategic Plan for Data Science: [https://datascience.nih.gov/sites/default/files/NIH\\_Strategic\\_Plan\\_for\\_Data\\_Science\\_Final\\_508.pdf](https://datascience.nih.gov/sites/default/files/NIH_Strategic_Plan_for_Data_Science_Final_508.pdf)

these strategies. These organizations also can assist in addressing core issues, such as data sharing, security, and privacy.

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

Numerous federal and non-governmental efforts are underway to establish CDEs for particular conditions, with the goal of improving accuracy, consistency, and interoperability among datasets from research on areas of health and disease. Agreeing on CDEs pertaining to clinical conditions experienced by pregnant women and lactating women, as well as relevant pregnancy outcomes and infant characteristics, may help to facilitate and accelerate research on drugs and biologics in use or in development.

- 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”):* To prevent duplicative efforts, the panel should first conduct a survey of current efforts to develop CDEs and definitions across HHS divisions and among professional societies and other stakeholders. For example, CDC has started to create CDEs for its surveillance and research systems; databases on pregnancy and births managed by CMS and DoD may also be informative. Relevant, ongoing efforts include but are not limited to:
- NICHD’s MFMU Network has developed a list of CDEs, including lactation data points, and obstetric definitions used across its studies.
  - NIH has established a NIH CDE Task Force, led by the National Library of Medicine<sup>59</sup>. CDEs that are developed can be searched in the CDE Repository.<sup>60</sup>
  - Complementing this trans-NIH effort, and because its mission covers so many rare conditions, NINDS oversees an extensive process of developing CDEs to facilitate clinical trials and other research, which might be informative for this effort. Identifying core data elements across these conditions allows for comparisons and meta-analyses across studies. Currently, NINDS’ contract allows for the development of one set of CDEs annually. Taking stakeholder input into account, NINDS prioritizes conditions for which to develop CDEs, looking at case report forms, definitions in the data dictionary, compilation of relevant international standards (required by the FDA) and international CDEs, if any.<sup>61</sup>
  - AHRQ maintains the State Inpatient Databases that allow maternal/child linkages and prospective follow-up.<sup>62</sup>

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<sup>59</sup> <https://www.nlm.nih.gov/cde/index.html>

<sup>60</sup> <https://cde.nlm.nih.gov/>

<sup>61</sup> <https://commondataelements.ninds.nih.gov>. See also How data become CDEs: <https://commondataelements.ninds.nih.gov/CDEStandard>; and Grinnon et al., 2012 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3513359/pdf/nihms421015.pdf>

<sup>62</sup> <https://www.hcup-us.ahrq.gov/sidoverview.jsp> ; <https://hcup-us.ahrq.gov/db/state/siddbdocumentation.jsp>

- ACOG recently led standardization efforts to harmonize definitions for the data elements used in obstetrics and gynecology.<sup>63</sup>
- 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.*
- 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.*

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<sup>63</sup> <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>

## PRGLAC Implementation Plan: Recommendation 13

### ***Rec. 13. Optimize registries for pregnancy and lactation***

Although some registries already exist for therapeutics used by pregnant women and lactating women, currently there is no centralized listing of these registries. The creation of such a data source would be resource intensive in time and cost, but of significant value. Steps should also be taken to optimize existing as well as newly developed registries to support the anticipated increase in pregnant and lactating women using therapeutics participating in research. The development of standardized reporting forms for these data will greatly facilitate making the information widely accessible and usable in a timely manner (see also Recommendations 11Ae and 2Ac).<sup>64</sup>

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

- a. Identify the elements needed for a registry listing:* A centralized, widely accessible pregnancy and lactation registry listing site or database would require a plan for its development and maintenance, including the following elements:
- Design: including issues such as who will enter and curate the data, and how to make it as user-friendly as possible while still obtaining necessary information
  - Budget: set-up and long-term
  - Logistics: who will host the registry site
  - Governance, policies, and content: what comprises a registry; who decides what types of registries will be included and what level of scientific rigor will be required; will government-funded registries be required to be listed
  - Maintenance plan: who is responsible for maintenance and what is the frequency of updates

This web-based registry site would include standardized information on each registry listed and should be searchable. Stakeholders should be offered an opportunity to provide input on the information most useful to them, such as the list of data fields or summaries of analyses conducted using registry data. Other questions to be considered include how to keep registry status and contact information up-to-date, whether pregnancy surveillance studies (or single-arm pregnancy safety studies) also should be included, and whether to remove a registry from the site if it closes (but possibly linking to a publication or summary resulting from the registry).

AHRQ developed options for a registry listing website (Registry of Patient Registries),

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<sup>64</sup> For a more complete listing and description of the registries that the PRGLAC Task Force considered in making this recommendation, see the PRGLAC report, p. 313 et seq.

which provide a useful template for costs and timeline.<sup>65</sup> Depending on the model chosen, AHRQ estimated that a registry listing website could cost several millions of dollars to establish, and approximately \$1 million to maintain each year.

- b. *Develop a public-private partnership to host a pregnancy/lactation registry listing website:* One approach to supporting and maintaining a website with a comprehensive listing of pregnancy/lactation registries would be to develop a public-private partnership (potentially through the FNIH) that includes partners (academic institutions, industry, government, professional societies and women’s health organizations) with experience and a stake in research on therapeutics and exposures of pregnant and lactating women. For example, the FDA already hosts a site listing pregnancy exposure registries that align with key elements according to agency guidance; the National Library of Medicine supports one such example of a public-private partnership, the LactMed website.<sup>66</sup>

### **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**
- a. *Convene a forum to develop registry standards and CDEs:* Building on previous efforts, gatherings of relevant stakeholders should be convened to come to consensus on preferred standards for pregnancy and lactation registries, and common data elements so that registry data can be interoperable. Such a forum should include federal agencies with experience in patient registries (FDA, AHRQ, CDC, NIH, among others), healthcare providers who serve pregnant women and lactating women, representatives of the pharmaceutical industry, electronic medical record companies, professional societies, and other organizations with registry experience (e.g., MotherToBaby,<sup>67</sup> Antiretroviral Pregnancy Registry [called “the ART registry” in the recommendations, but correctly identified as APR], North American Antiepileptic Drug Pregnancy Registry). A forum that includes the necessary participants could be convened within 1 year to 18 months.

Among the issues for consideration by forum participants are:

- Governance structure for this set of common data elements, including what entity would “own” it, how it would be updated and by whom
- Identification of resources for development and maintenance, and potential funders
- Whether use of these elements can be mandatory, or if not, how to encourage uptake across sectors

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<sup>65</sup> <https://effectivehealthcare.ahrq.gov/products/registry-of-patient-registries/abstract>; note that AHRQ worked with [clinicaltrials.gov](https://clinicaltrials.gov) to add a registry sub-type to that listing. In 2019, 47 U.S. pregnancy registries were listed.

<sup>66</sup> <https://www.ncbi.nlm.nih.gov/books/NBK501922/>

<sup>67</sup> <https://mothertobaby.org/pregnancy-studies>

- Best practices for obtaining information in real time from pregnant women, lactating women, and healthcare professionals/prescribers, such as chart abstraction within a network of clinical sites
  - What incentives might be offered to encourage the provision of information
- b. Compile materials for use by forum participants that reflect current knowledge and experience in establishing measures and common data elements for registries:* Such information could include, but not be limited to, the following resources:
- AHRQ current registries handbook with checklist of best practices/registry standards (including pregnancy registries)<sup>68</sup>
  - AHRQ report on its registry outcome measure harmonization project<sup>69</sup>
  - NIH CDEs Task Force and repository<sup>70</sup>
  - ACOG Electronic Medical Record
  - PCORI Trust Fund’s Strategically Coordinated Women’s Health Registry Network (data element harmonization)<sup>71</sup>
  - FDA’s Draft Guidance for Post-Approval Pregnancy Studies<sup>72</sup>
- c. Create standardized templates for information:* Using the consensus registry standards and CDEs, work with EHR companies to create standardized templates for this information. These templates should be able to link to maternal and child health datasets when exported.
- d. Meet with professional societies to encourage use of these standardized templates:* Encourage uptake of these templates as the practice standard for data collection/reporting.
- e. Explore additional long-term data collection on therapeutics used by pregnant women and lactating women:* Consider partnering with ongoing longitudinal studies that are, or could be, collecting medication exposures in pregnant or lactating women, and long-term outcomes in children (e.g., the NIH Environmental Influences on Child Health Outcomes study, the IMI 2 ConcePTION project).

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<sup>68</sup> <https://effectivehealthcare.ahrq.gov/products/registries-guide-3rd-edition/research>

<sup>69</sup> <https://effectivehealthcare.ahrq.gov/products/registry-of-patient-registries/outcome-measures-framework>

<sup>70</sup> <https://www.nlm.nih.gov/cde/index.html>

<sup>71</sup> <https://aspe.hhs.gov/developing-strategically-coordinated-registry-network-crn-womens-health-technology>

<sup>72</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry> . When finalized, this guidance will reflect FDA’s current thinking on this issue.

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

- **Use the ART<sup>73</sup> registry as a model**
  - a. *Identify and emulate agencies/stakeholders that already have strong data sharing policies:* Federal agencies and other organizations already share data from their registries; the existence of these datasets needs to be widely disseminated, including how to access them. The Antiretroviral Pregnancy Registry<sup>74</sup> (called “the ART registry” in the recommendations, but correctly identified as APR) publicly posts results every 6 months. The AHRQ handbook includes extensive discussion about governance procedures, such as access to data.
  - b. *Develop a data-sharing plan:* Federal data-sharing policies and plans, such as those developed by AHRQ, can provide an outline for what components should be included in a data sharing plan, such as:
    - Costs to facilitate data access (money, staff, materials)
    - IRB issues (patient protections, confidentiality)
    - Ownership and governance
    - Validation of the data and by whom
    - Data use agreement policies
    - Legal issues (disclaimers, HIPAA/privacy issues)
    - Publication rights
  - c. *Consider partnering with data quality improvement programs:* For example, HRSA is funding ACOG to implement a program on state-based evaluation of outcomes in pregnancy, a quality improvement data collection initiative called the Alliance for Innovation on Maternal Health.

### 13D. Develop disease-/condition-focused registries

- **Move toward a single registry for all therapeutic products with input from stakeholders**
  - 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:* The members of the public-private partnership, cited in Recommendation 13A, using the agreed upon registry standards and CDEs developed under Recommendation 13B, should develop a plan for reaching out more broadly to additional pharmaceutical manufacturers about a potential collaborative

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<sup>73</sup> Note: The 2018 PRGLAC Task Force report should have written “APR”: <https://fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries>

<sup>74</sup> <https://www.apregistry.com/Default.aspx>



registry. Ideally, this registry would comprise a single site that includes therapeutics used for the diseases/conditions that pregnant and lactating women may have. The IMI 2 ConcePTION project could provide a model for this outreach effort. Initial meetings could focus on understanding what obstacles might exist to developing widely available disease-/condition-focused registries from the industry perspective, such as proprietary data concerns, and approaches to overcome those obstacles.

Alternatively, a distributed data model could be considered, in which independent registries and data systems (apps, EHRs) would work with the agreed upon CDEs, with a data coordinating center established to respond to specific queries. Several models exist for this approach, including PCORI and the FDA's Sentinel program.

- b. Expand the use of disease/condition post-marketing studies:* To address enrollment challenges encountered in single-drug pregnancy registries issued as post-marketing requirements by the FDA, there is a need to consider other strategies, such as disease/condition based registry post-marketing studies to obtain needed safety information in drugs used during pregnancy and/or lactation, including lactation substudies to assess exposure and safety for breastfed infants.

## **PRGLAC Implementation Plan: Recommendation 14**

***Recommendation 14. The HHS Secretary should consider exercising the authority provided in law to extend PRGLAC when its charter expires in March 2019.***

On March 13, 2019, the HHS Secretary formally extended PRGLAC's charter for 2 years, until March 13, 2021. The charter directs the Task Force with providing guidance on the implementation of the recommendations made in its 2018 report.

## **PRGLAC Implementation Plan: 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***

PRGLAC is a formal advisory committee constituted under the Federal Advisory Committee Act. Recommendation 15 of its 2018 report to the Secretary and to Congress called for an additional advisory body to monitor implementation of the recommendations, so consideration was deferred until PRGLAC developed an implementation plan for the other recommendations. However, the current PRGLAC recommends that, once its charter expires in 2021, another committee with a similar range of expertise should be established to ensure that the steps recommended by PRGLAC are implemented and progress is monitored.

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### ***Working Group 1: Research and Training***

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## APPENDIX 2: Clinical Research Networks

### *Clinical Research Networks Specific to Research for Pregnant Women and Lactating Women*

The [Maternal-Fetal Medicine Units \(MFMU\) Network](#), funded by NICHD, is designed to support well-designed clinical trials in maternal-fetal medicine and obstetrics. Current studies include:

- An investigation of pravastatin to prevent preeclampsia ([NCT03944512](#))
- A randomized controlled trial to assess whether treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) in pregnancy results in a reduction in the rate of hypertensive disorders of pregnancy ([NCT03487185](#))
- A randomized placebo-controlled trial to assess whether tranexamic acid as prophylaxis lowers the risk of postpartum hemorrhage in women undergoing a cesarean delivery ([NCT03364491](#))
- A randomized trial to determine whether the Arabin pessary is a useful intervention of preterm birth at less than 37 weeks in women with a singleton gestation and a short cervix ([NCT02901626](#))
- A randomized trial evaluating the use of micronized vaginal progesterone or pessary versus placebo to prevent early preterm birth in women carrying twins and with a cervical length of less than 30 millimeters ([NCT02518594](#))
- A randomized Phase I/II study of the safety and immunogenicity of a single dose of the recombinant live-attenuated Respiratory Syncytial Virus (RSV) vaccines ([NCT03916185](#))
- A study to determine whether treating pregnant women who have a primary cytomegalovirus (CMV) infection with CMV antibodies will reduce the number of babies infected with CMV ([NCT01376778](#))
- Follow-up observational studies of children in an earlier study of antenatal corticosteroids to assess cognitive function and pulmonary complications in childhood
- An observational study of hepatitis C virus in pregnancy

The [International Maternal, Pediatric, Adolescent AIDS Clinical Trials \(IMPAACT\)](#) Network (funded by the National Institute of Allergy and Infectious Diseases, NICHD, and the National Institute of Mental Health) focuses on potential therapies for HIV and other infections and related symptoms in infants, children, adolescents, and pregnant and lactating women. Among current studies are:

- Phase III study of the virologic efficacy and safety of dolutegravir-containing versus efavirenz-containing ART regimens in HIV-1-infected pregnant women and their infants



- Phase I/II trial of the PK, tolerability, and safety of once-weekly rifapentine and isoniazid in HIV-1-infected and HIV-1-uninfected pregnant and postpartum women with latent tuberculosis infection
- PK properties of ART, anti-tuberculosis, contraceptive, and related drugs during pregnancy and postpartum
- An assessment of PK, feasibility, acceptability, and safety of oral pre-exposure prophylaxis for primary HIV prevention during pregnancy and postpartum in adolescents and young women and their infants

The [Collaborative Ambulatory Research Network \(CARN\)](#) project, funded by HRSA, surveys healthcare providers that provide clinical services to women. CARN study questionnaires are designed to generate descriptive data pertaining to obstetrician-gynecologists' practice patterns, clinical experiences, basic knowledge, professional training, access to resource materials, and educational needs. Study findings are disseminated within ACOG and through publications. Some recently published studies include survey data on:

- The variation in waiting period for Medicaid postpartum sterilizations
- Provider and patient knowledge and views of office practices on weight gain and exercise during pregnancy
- Umbilical cord clamping practices
- Opioid knowledge and prescribing practices among obstetrician-gynecologists

HRSA's related [Pregnancy-Related Care Research Network \(PRCRN\)](#) is a national collective of practicing obstetricians-gynecologists that collects survey data pertaining to provider practice patterns, clinical experiences, basic knowledge, professional training, access to resource materials, and educational needs. In addition, the PRCRN provides the opportunity for office-based research on clinical outcomes.

The [Global Network for Women's and Children's Health Research](#), funded by NICHD, supports and conducts clinical trials in resource-limited countries by pairing foreign and U.S. investigators, with the goal of evaluating low-cost, sustainable interventions to improve maternal and child health and simultaneously building local research capacity and infrastructure. Some current studies include:

- A randomized, placebo-controlled clinical trial at eight research sites in Latin America, South Asia, and sub-Saharan Africa to assess whether a single, prophylactic intrapartum oral dose of 2g azithromycin given to women in labor will reduce 1) maternal death or sepsis, and 2) intrapartum/neonatal death or sepsis
- A study to test whether a nutritional intervention, commencing at least 3 months before conception, is associated with a greater newborn length compared to offspring whose mothers received the same intervention at 12 weeks gestation or not at all

- A prospective, randomized, placebo-controlled clinical trial to examine whether low-dose aspirin initiated between 6 0/7 weeks and 12 6/7 weeks gestation reduces the risk of preterm birth

The [Obstetric-Fetal Pharmacology Research Centers \(OPRC\) Network](#), funded by NICHD, supports specialized research to improve the safety and efficacy of medication use during pregnancy and while breastfeeding. These projects include basic/translational research involving cells and/or animals, as well as clinical studies involving humans. Some current projects include:

- An opportunistic study to develop guidelines to determine the optimal use of Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants (i.e., sertraline, fluoxetine, citalopram/escitalopram) in 200 pregnant women already taking SSRI antidepressants ([NCT02519790](#))
- Research to determine the maternal-fetal plasma concentrations and pharmacogenetic characteristics associated with neonatal SSRI discontinuation syndrome
- An investigation of the impact of genomic variability on inter- individual difference in SSRI dosing, plasma concentrations, and PK during pregnancy, focusing on genes involved in the metabolism and elimination of SSRIs, drug transporters responsible for SSRI access to the central nervous system, and genes encoding critical SSRI targets involved in therapeutic efficacy
- An opportunistic evaluation of sublingual buprenorphine (BUP) in pregnant women already taking BUP for opioid addiction to define the PK of BUP and determine whether there is a better way to gauge dosing based on objective, physiological parameters, and to define neonatal exposure to BUP through human breastmilk ([NCT02863601](#))
- A phase I, double-blinded, randomized controlled trial to evaluate the maternal-fetal safety and PK profiles of pravastatin (20 mg/day) when used in pregnant women at high-risk of developing preeclampsia ([NCT01717586](#))
- A pilot study to determine the transplacental transfer of existing (marketed) and emerging nanoparticle formulations containing doxorubicin

[Practice-based research networks \(PRBNs\)](#) are groups of primary care clinicians and practices working together to answer community-based healthcare questions and translate research findings into practice. AHRQ maintains a registry of PBRNs. This searchable registry identified dozens of [PBRNs that expressed interest in research related to pregnancy, childbirth, and neonatology](#).

The [Centers for Birth Defects Research and Prevention \(CBDRP\)](#), funded by CDC, collaborates on population-based case-control studies of birth defects and stillbirth. Interview questions include a broad array of maternal conditions, and detailed questions about the treatments, such as prescription and over-the-counter medications, as well as lifestyle factors.

The [Perinatal Quality Collaboratives \(PQCs\)](#), funded by CDC, are state or multistate networks of multidisciplinary teams working to improve outcomes for maternal and infant health by advancing evidence-informed clinical practices and processes using quality improvement principles. PQCs address gaps by working with clinical teams, experts and stakeholders, including patients and families, to spread best practices, reduce variation in care and optimize resources to improve perinatal care and outcomes.

***Clinical Research Networks Not Specific to Pregnancy or Lactation Research, but Open to Partnerships with Outside Investigators***

The [Clinical and Translational Science Awards \(CTSA\) Program](#), funded by the National Center for Advancing Translational Sciences (NCATS), supports more than 50 medical research institutions across the nation. CTSA Program support enables research teams including scientists, patient advocacy organizations, and community members to tackle system-wide scientific and operational problems in clinical and translational research that no one team can overcome. Program goals are to:

- Train and cultivate the translational science workforce
- Engage patients and communities in every phase of the translational process
- Promote the integration of special and underserved populations in translational research across the human lifespan
- Innovate processes to increase the quality and efficiency of translational research, particularly of multisite trials
- Advance the use of cutting-edge informatics

The [Trial Innovation Network](#), also funded by NCATS under the CTSA umbrella, was developed to address critical roadblocks in clinical trials. The network's three centers provide expertise to researchers nationally who wish to collaborate. The program focuses on operational innovation, operational excellence and collaboration while leveraging the expertise, diversity, and broad reach of the CTSA Program. Features include master contracting agreements, quality-by-design approaches, and a focus on evidence-based strategies to recruitment and patient engagement. The goal is not only to execute trials better, faster and more cost-efficiently, but also to be a national laboratory to study, understand and innovate the process of conducting clinical trials.

The primary goal of the National Human Genome Research Institute [EMR and Genomics \(eMERGE\) Network](#) is to develop, disseminate, and apply approaches to research that combine biorepositories with electronic medical record (EMR) systems for genomic discovery and genomic medicine implementation research. External institutions may apply for affiliate membership to the eMERGE Network to collaborate with the network on studies.

The [Institutional Development Awards \(IDeA\) States Pediatric Clinical Trials Network](#)'s overarching goals are to provide access to state-of-the-art clinical trials to medically underserved

and rural populations in the priority areas, including pre-, peri-, and postnatal outcomes, neurodevelopment, and overall health.

The [Network for Excellence in Neuroscience Clinical Trials \(NeuroNEXT\)](#) was created by NINDS to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry. The network provides an infrastructure to facilitate the rapid development and implementation of protocols in neurological disorders, in both adult and pediatric populations. Individual investigators who want to collaborate with NeuroNEXT bring additional funding for their specific project.

The [Experimental Therapeutics Clinical Trials Network \(ETCTN\)](#) PK Resource Laboratories (PK Laboratories), funded by the National Cancer Institute (NCI), support sites within NCI's ETCTN. The PK Laboratories organize specimen collection and subsequent analysis of pharmacokinetic endpoints, drug-drug interactions, cytochromes P450 (CYP) interactions, and food effects in ETCTN studies of NCI Investigational New Drug (IND) agents. The research objective of the ETCTN is to support the early-stage clinical development of novel cancer treatments that include NCI IND agents based on sound preclinical findings, consistent with national priorities for developmental therapeutics clinical cancer research.

### ***Other Potential Resources for Research Infrastructure***

[MotherToBaby](#), a service of the non-profit OTIS, is funded by HRSA as well as by state-based funding sources, including hospitals or academic institutions, departments of health and state departments of education. The service provides evidence-based information to mothers, healthcare professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding. The website provides an opportunity for pregnant or lactating women to register if they are interested in participating in observational studies. The MotherToBaby network also has a national research infrastructure established to conduct longitudinal pregnancy and lactation medication and vaccine exposure safety studies. These studies are supported by a combination of industry and federal funding.

The [Global Pregnancy Collaboration \(CoLab\)](#), funded by the Bill and Melinda Gates Foundation, is designed to improve the health of mothers and their infants by facilitating harmonized perinatal data management and collaborative research. This is accomplished by developing standardized generic data dictionaries that cover the needs of all maternal-child healthcare, from the simplest in the most resource-poor countries to the most sophisticated research in more privileged areas.

NCATS' [DIAMOND portal](#) brings training resources together in one place for clinician-scientists. The portal includes training materials in eight different competency domains, ranging from the specifics of running trials to more general topics, such as leadership. The portal also includes assessments that study teams can use to check that staff members are adequately trained.

The NCATS [Smart IRB Platform](#) provides a harmonized (i.e., consistent) approach to IRBs. The platform can be used by any clinical research network or even a single investigator wishing to

conduct a multisite clinical study. [Resources](#) include authorization and joinder agreements, guidance, communications plans, implementation checklists, model language, and others. The platform currently does not include resources specific to regulation of studies involving pregnant women and lactating women.

### APPENDIX 3: PRGLAC Implementation Plan Process

The 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to provide advice to the Secretary of Health and Human Services (HHS) regarding the gaps in knowledge and research on safe and effective therapies used by pregnant women and lactating women. The PRGLAC Task Force submitted its report to the Secretary in September 2018.<sup>75</sup> In March 2019, the Secretary formally extended PRGLAC's charter for two years, until March 2021. For the next phase of its work, PRGLAC was tasked with providing guidance on the implementation of the Task Force's recommendations. The Task Force met four times during the extended charter period in order to establish working groups, develop the implementation plan, and foster discussion and collect comments on said implementation plan.

Task Force membership remained largely the same for the second phase. The Secretary appointed some new federal members to replace those who left government service or changed federal positions. In addition, during PRGLAC's deliberations it became clear that many pregnant women and lactating women are using dietary supplements with inadequate information, so the Secretary determined that it was appropriate to appoint a new federal member from the National Center for Complementary and Integrative Health, NIH, designated by the Center's Director, to provide that expertise.

The first meeting of Task Force to launch the implementation phase was held by public webinar in May 2019. The Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Dr. Diana Bianchi, who serves as Chair, charged the Task Force with developing more detailed plans for implementation of the 15 recommendations laid out in the 2018 PRGLAC Report. She announced the establishment of four working groups: Working Group 1: Research/Training; Working Group 2: Regulatory; Working Group 3: Communication; and Working Group 4: Discovery. Each Task Force member was assigned to a working group and co-chairs appointed. The Chair invited all meeting participants, including the public attendees, to send nominations of subject matter experts to fill in missing expertise in the working groups.

From the nominees submitted, the Chair selected *ad hoc* working group members based on the experience needed in each working group to address the recommendations. The *ad hoc* members were invited to attend the August 2019 meeting and participate in one of the working groups.

An in-person meeting of the Task Force, open to the public and available by videocast, was held in August 2019. Each working group was charged with creating an implementation plan for their assigned recommendations that addressed the following areas:

- Steps needed to address each recommendation
- Whether those steps have started

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<sup>75</sup> <https://www.nichd.nih.gov/about/advisory/PRGLAC>

- What agencies and stakeholders should be involved
- A plan for implementing each step if feasible
- If any new programs should be established or existing programs expanded.

At the end of the August 2019 meeting, working group co-chairs presented summaries of their initial discussions. Public comments from stakeholders were also welcomed. As in previous Task Force meetings, audience participants were encouraged to comment and join the discussion. Each working group was provided support from one or more NICHD staff to conduct discussions through a series of webinars throughout the fall of 2019, with the goal of presenting their findings on implementing the PRGLAC recommendations at the February 2020 Task Force meeting.

From September 2019 to January 2020, the four working groups each held five webinars to discuss the steps needed to implement their assigned recommendations.<sup>76</sup> In some cases, additional subject matter experts were asked to join these discussions to address specific topics and answer questions. Participating experts included representatives from HHS's Office of Human Research Protections, the *All of Us* Research Program, NIH's and the Food and Drug Administration's Best Pharmaceuticals for Children Act (BCPA) programs, an NICHD-funded researcher, and a legal representative from the pharmaceutical industry. Two additional webinars were scheduled for all interested working group members to attend. These topics addressed NIH's BCPA program and NCATS's Clinical and Translational Science Awards (CTSA) Program.

The first PRGLAC meeting of 2020, again open to the public and available by videocast, was held on February 3. Each working group presented its findings, followed by robust discussion by the entire Task Force. Meeting attendees also were encouraged to participate. All presentations are available on the PRGLAC website.

The draft implementation plan was based on working group discussions, prepared worksheets, presentations made during in-person meetings, and public comments. Task Force members and *ad hoc* working group members were sent each recommendation implementation summary for review and comment. Comments were incorporated into the implementation plan, which was discussed at the PRGLAC meeting on June 24, 2020, and was open to the public. After a further period of comment by Task Force members, the plan was finalized. Each PRGLAC member stated concurrence on the PRGLAC Implementation Plan (or in a few instances, non-

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<sup>76</sup> **Working Group 1:** September 20 (11:00-12:30 pm); September 20 (3-4:30 pm); October 1 (1:30-3:00 pm); November 22 (1:00-2:30 pm); and December 6 (2:00-3:30 pm); **Working Group 2:** October 2 (10-12 pm); November 5 (2:00-4:00 pm); November 25 (1:00-3:00 pm); December 3 (1:00-3:00 pm); and January 6 (2:00-4:00 pm); **Working Group 3:** September 27 (9:00-10:00 am); October 25 (4:00-5:00 pm); November 18 (2:00-3:00 pm); December 19 (11:00 am-12:00 pm); and January 15 (1:00-2:00 pm); **Working Group 4:** October 2 (2:00-3:00 pm); October 22 (12:00-1:30 pm); November 1 (3:30-5:00 pm); December 2 (3:00-4:00 pm); and January 10 (1:00-3:00 pm)

concurrence with specific steps) by email to the Executive Secretary, and the plan was submitted to the HHS Secretary in late summer 2020, as requested.



## **APPENDIX 4: List of Acronyms Used in the Plan**

ACA: Affordable Care Act

ACNM: American College of Nurse Midwives

ACOG: American College of Obstetricians and Gynecologists

AHRQ: Agency for Healthcare Research and Quality

ART Registry: Antiretroviral Pregnancy Registry (APR), incorrectly listed as “the ART registry” in PRGLAC recommendations

AWHONN: Association of Women’s Health, Obstetric, and Neonatal Nurses

BARDA: Biomedical Advanced Research and Development Authority

BPCA: Best Pharmaceuticals for Children Act

BRPD: Society for Birth Defects and Research Prevention

CARN: Collaborative Ambulatory Research Network

CBDRP: Centers for Birth Defects Research and Prevention

CDC: Centers for Disease Control and Prevention

CDEs: Common Data Elements

CME: Continuing Medical Education

CMS: Centers for Medicaid and Medicare Services

CTSAs: Clinical and Translational Science Awards

CUDDLE Study: Commonly Used Drugs During Lactation and Infant Exposure Study

DASH: Data and Specimens Hub

DoD: U.S. Department of Defense

EHRs: Electronic Health Records

EMRs: Electronic Medical Records ETCTN: Experimental Therapeutics Clinical Trials Network

FDA: Food and Drug Administration

FNIH: Foundation for NIH

FOAs: Funding Opportunity Announcements

HHS: – U.S. Department of Health and Human Services

HIPAA: Health Insurance Portability and Accountability Act

HRSA: Health Research and Services Administration

ICs: NIH Institutes and Centers

IMI 2 ConcePTION: Innovative Medicines Initiative on Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology, and Breastfeeding to Improve Outcomes Now

IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials

INCLUDE: INvestigating Co-occurring conditions across the Lifespan to Understand Down SyndromE

IRB: Institutional Review Board

MFMU: Maternal-Fetal Medicine Units Network

NCATS: National Center for Advancing Translational Sciences

NCCIH: National Center for Complementary and Integrative Health

NCHS: National Center for Health Statistics

NCI: National Cancer Institute

NHGRI: National Human Genome Research Institute

NHLBI: National Heart, Lung, and Blood Institute

NIAID: National Institute of Allergy and Infectious Diseases

NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases

NIGMS: National Institute of General Medical Sciences

NIH: National Institutes of Health

NINDS: National Institute of Neurological Disorders and Stroke  
NIMH: National Institute of Mental Health

OB-GYN: Obstetrician-Gynecologist

OHRP: Office of Human Research Protections, HHS

OPRCs: Obstetric and Pediatric Pharmacology Research Centers

ORWH: Office of Research on Women's Health, NIH

OTIS: Organization of Teratology Information Specialists

PBRNs: Practice-Based Research Networks

PCORI: Patient-Centered Outcomes Research Institute

PD: Pharmacodynamic

PK: Pharmacokinetic

PKPB: Physiologically based pharmacokinetic

PLLR: Pregnancy and Lactation Labeling Rule (FDA)

PQCs: Perinatal Quality Collaboratives

PRCRN: Pregnancy-Related Care Research Network

PREA: Pediatric Research Equity Act

PRGLAC: Task Force on Research Specific to Pregnant Women and Lactating Women

PTN: Pediatric Trials Network

SMFM: Society for Maternal-Fetal Medicine

SUCCESS: Knowledge Strengthening Use, Capacity, Collaboration, Exchange, Synthesis, and Sharing program VA: Department of Veterans Affairs

VICP: Vaccine Injury Compensation Program

WHO: World Health Organization

WRHR: Women's Reproductive Health Research Career Development Program