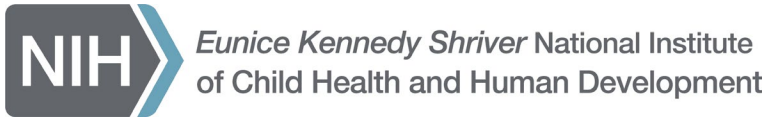
PRGLAC Working Group 4

Implementation Steps for Recommendations 9, 10, and 12



Recommendation 9

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

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

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

- Policy makers might consider making amendments to existing legislation, e.g. the Federal Food, Drug, and Cosmetic Act that would authorize HHS to establish new and separate processes for the identification, **prioritization**, and study of therapeutics for conditions **specific** to pregnant women and lactating women.

- More specifically, this approach would create a new and separate process for prioritizing the study, development, and manufacture of new drugs and therapeutics for conditions experienced specifically by pregnant and lactating women, such as hyperemesis, preterm labor, low milk supply, mastitis, and perinatal mood disorders.

- The new legislation/program could look like the *Best Pharmaceuticals for Children Act (BPCA)* which was created to increase the number of therapeutics prescribed/used for children.

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

To create a separate prioritization process for the studying of drugs used/needed by pregnant women and Lactating women- the following steps could be taken:

- *Identification of a lead agency* to coordinate the prioritization process and research efforts across the Federal government (and/or across NIH Institutes and Centers)
- *Make public a request for nominations* – The lead agency (e.g. NICHD) would publish two lists of research needs for 1) pregnant women and 2) lactating women and then
- *Request nominations for drugs/therapeutics* that are used to treat conditions faced by pregnant and lactating women but don't have adequate dosing, safety, or efficacy data.

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

- *Post the nominations on a (e.g. NICHD) website* and in the Federal Register, along with outreach to professional societies and other key stakeholders.
- *Obtain stakeholder input on nominations* – Groups including researchers, clinicians, consumer advocates, payers, and patient/family organizations nominate therapeutic areas and pediatric drug needs for consideration.
- *Review of Nominations* – Lead agency (e.g. NICHD's Obstetric and Pediatric Pharmacology and Therapeutics Branch and/or Pregnancy and Perinatology Branch) oversees/coordinates a careful review of the nominations using a range of criteria.

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

- *Review of Nominations* –nominations could be reviewed using a range of criteria scored on the following:
  - ***Evidence*** – existence of an unmet need and/or gaps in the available evidence
  - ***Feasibility*** – consideration of the resources available to conduct the study (number of patients, sites, expertise of primary investigator) and ability to implement findings
  - ***Urgency*** – immediacy of the obstetrical or lactation needs for this drug
  - ***Impact*** – potential for impact on disease prevalence, severity of the condition to be treated, potential cost of therapeutics, frequency of use, and availability of alternative treatments
- *Finalize the List of Priority Needs in Therapeutics for Pregnant & Lactating Women* – The lead agency (e.g. NICHD) finalizes the list of priority needs, posts on its website, and publishes the list in the Federal Register.

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

- To facilitate the clinical development of therapeutics for pregnant women and lactating women from phase I to phase II, it is essential to **mitigate the issues of liability** and **identify incentives**.

- **New legislation is likely required** that incorporates the following elements/sections from three existing authorities/programs:

  - From the **NIH Vaccine Research Center (VRC)** – The new PRGLAC research program could, like NIH's VCR, function as a public (NIH) version of a private sector biotechnology entity,

  - From **BARDA** – Give HHS (NIH, FDA, or a new office) the authority to provide funding to investigators/sponsors to incentivize continued research and development of therapeutics that address the needs of pregnant and lactating women from phase 1 to phase 2 trials and beyond.

  - From the **Best Pharmaceuticals for Children Act (BPCA)** – Provide drug manufacturers with marketing exclusivity to conduct phase 2 and beyond studies of therapeutics that address the needs of pregnant and lactating women.

Take-aways for Recommendation 9

Creating a separate prioritization processes for pregnant women and lactating women will likely require new legislation or the amending of existing legislation, e.g. the Federal Food, Drug, and Cosmetic Act.

The new/amended legislation could create a new program and implement steps similar to those created by NICHD for the implementation of *Best Pharmaceuticals for Children Act (BPCA).*

To facilitate the clinical development of therapeutics for pregnant women and lactating women from phase I to phase II, it is essential to **mitigate the issues of liability** and **identify incentives**.

To effectively mitigate issues of liability and to incentivize the progression of clinical development from phase I to II, new legislation is likely required that incorporates elements of three existing programs: NIH VRC, BARDA, and the BPCA.

Recommendation 10

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

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

- To ensure that investigators/sponsors specifically justify exclusion of pregnant women and lactating women in their study designs **new legislation is likely required**- similar to the Pediatric Research Equity Act (PREA)- that amends the Federal Food, Drug, and Cosmetic Act to:

  Authorize the FDA to **require** investigators/sponsors who submit an application for a drug or biological product- that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration- to submit a "PRGALC Assessment" and "PRGLAC Study Plan."

PRGLAC Assessment & Study Plan

PRGLAC assessment

Similar to the pediatric assessment required by the PREA, a PRGLAC assessment would contain data gathered from PRGLAC studies specific to each phase (month, trimester) of pregnancy and during lactation.

PRGLAC Study Plan

A PRGLAC Study Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/ pharmacodynamics, safety, and efficacy) that the applicant plans to conduct. Similar to the Pediatric Study Plan, a PRGLAC Study Plan is a statement of intent that outlines the studies (e.g., pharmacokinetics/ pharmacodynamics, and safety in pregnant women and lactation studies) that the applicant plans to conduct.

Address Current Barriers to Including Pregnant & Lactating Women in Clinical Trials

New legislation should also address the following current barriers to including pregnant women in clinical trials.

- Currently federal regulations do not define “acceptable risk” to a woman or fetus- and this serves as a barrier to the inclusion of pregnant and lactating women in clinical research.
- Legal risk perceived by investigators/sponsors if the mother or fetus experiences an adverse outcome. This barrier could be addressed by standardizing the existing informed consent process. Studies enrolling pregnant women could develop a uniform consent process that provides guidelines for counseling potential enrollees on how an intervention will be assessed for effectiveness, safety parameters, and stopping rules.

Steps that could be taken outside of those required by statute

- To make the shift toward **inclusion pregnant women and lactating women in their study designs as the default** when exclusion cannot be justified, IRBs may need practical guidance on how to apply the regulations and how to specifically weigh risks and benefits to ensure the ethical acceptability of research with pregnant women as participants

- This could be done by providing IRBs with an operational framework to assist in their ethical analysis to 1) favor inclusion of pregnant women in clinical research and 2) to provide appropriate protections.

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

- As discussed above legislation is likely required (again, similar to the PREA) that authorizes the FDA to require sponsors/primary investigators of new drugs or biologics to submit "**PRGLAC study plans**" (analogous to PREA required "pediatric study plans").
- A *PRGLAC Study Plan* is a statement of intent that outlines the PRGLAC studies (e.g., pharmacokinetics/ pharmacodynamics, safety, and lactation) that the applicant plans to conduct.
- For example, "PRGLAC study plans" should detail how the sponsor/primary investigator plans to assess the influence of pregnancy- and the different stages of pregnancy- and lactation on the pharmacokinetics (PK)/ pharmacodynamics (PD) of the proposed drugs or biologic products.

Use of FDA draft guidance on “Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials”

In April 2018, the FDA published draft guidance for industry on “Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials” and included guidance that investigators/sponsors could consider when designing clinical trial that includes pregnant women, e.g. for inclusion in a PRGLAC study plan:

- *Because of the extensive physiological changes associated with pregnancy, PK parameters may change, sometimes enough to justify changes in dose or dosing regimen. For drug development programs where there are plans to enroll pregnant women in a phase 3 clinical trial, PK data in pregnant women should be collected during the phase 2 clinical trials to guide appropriate dosing in phase 3. In situations where pregnant women are enrolled in phase 3 clinical trials for a marketed drug, PK data should be collected as part of the trial.*

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

- As discussed above legislation is likely required (similar to the PREA) that authorizes the FDA to **require** sponsors/primary investigators of new drugs or biologics to submit- at the time their application is submitted to FDA- a **PRGLAC assessment**.
- Similar to the pediatric assessment as required by the PREA, a PRGLAC assessment would contain data gathered from PRGLAC studies using appropriate formulations specific to each phase (month, trimester) of pregnancy and during lactation

Data for Pregnant & Lactating Women Obtained through Required PRGLAC Assessments

The data included in a PRGLAC assessment would have to adequately:

- Assess the safety of the drug or the biological product for the claimed indications **in all phases of pregnancy and during lactation**
- Support dosing and administration during and throughout pregnancy and during lactation for which the drug or the biological product has been assessed to be safe and effective

Investigators/sponsors would **be required to submit their PRGLAC assessments at the time their application is submitted to FDA**, *unless the requirement for the assessment has been deferred or waived*.

Inclusion of PK, PD, and Safety Studies in Required PRGLAC Study Plans

PRGLAC Study Plan

- The proposed new legislation would also authorize FDA to require sponsors/primary investigators to submit “PRGLAC study plans” (analogous to PREA required “pediatric study plans”) in which the applicants would detail how they plan to design and conduct **pharmacokinetics**, **pharmacodynamics**, **safety**, studies in pregnant women.

- For example, “PRGLAC study plans” should detail how the sponsor/primary investigator planned to assess the influence of pregnancy, and/or various stages of pregnancy, and lactation on the pharmacokinetics (PK)/ pharmacodynamics (PD) of the proposed drugs or biologic products.

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

In 2017 the Federal Policy for the Protection of Human Subjects, known as **the Common Rule**, was revised so removing the category of pregnant women as a "vulnerable population"

While the Common Rule permits pregnant women to decide if they want to participate in clinical research under appropriate conditions Institutional Review Boards (IRBs) may still be reluctant to allow them to do so.

To make the shift toward **inclusion as the default** when exclusion cannot be justified, IRBs may need practical guidance on how to apply the regulations and how to specifically weigh risks and benefits to ensure the ethical acceptability of research with pregnant women as participants

Guidance for Institutional Review Boards and Investigators

This could be done by providing IRBs with an operational framework to assist in their ethical analysis to 1) favor inclusion of pregnant women in clinical research and 2) to provide appropriate protections. Such an operational framework could be provided through the following steps:

- Include experts in obstetrics and maternal-fetal medicine as regular IRB members;
- Interpret traditional ethical principles in a manner that justifies, rather than presumes, exclusion;
- incorporate the regulatory conditions of subpart B of the Common Rule to specifically justify the exclusion of pregnant women; and
- Consider additional safety monitoring to ensure that regulatory protections are met.

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

In April 2018 the FDA published draft guidance that included recommendations about how and when to include pregnant women in clinical trials for drugs and biological products **and** women who **become pregnant while enrolled** in a clinical trial:

When a pregnancy has been identified during a clinical trial, unbinding 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 299 additional risk-benefit considerations.

Require sponsors/investigators to include these plans in their PRGLAC study plans

- The recommendations included in the FDA guidance document are nonbinding and FDA states that this guidance for industry does not establish legally enforceable responsibilities- further highlighting the need for this guidance to be codified in new legislation.

- Sponsors/investigators of new drugs and therapeutics could be required to include this plan for if/when women become pregnant during the clinical study in their **PRGLAC study plan**, as required by the new/amended legislation discussed above.

Take-aways for Recommendation 10

The information provided in this guidance applies to drugs indicated to treat pregnancy specific conditions (e.g., preterm labor, pre-eclampsia), but the larger focus is on drugs indicated for conditions that occur commonly among females of reproductive potential.

Women in this group may require treatment for chronic disease or acute medical problems, and may become pregnant multiple times during the reproductive phase of their lives.

To implement the multiple components of Recommendation 10 new legislation will likely be required that authorizes the FDA to require investigators/sponsors to submit PRGLAC Assessments and Study Plans that include data, protocol development, and study designs specific to the needs to pregnant and lactating women.

Recommendation 12

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

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

Steps needed to implement this recommendation:

- Develop collaborative public-private structure with stakeholders involved in developing platforms for EHR and organizations that use EHRs
- Develop an optimal set of variables and make those widely available for systems to incorporate and to achieve consistency.
- Develop and implement a universal standard (**credentialing**) protocols that will harmonize methods for mother/infant EHRs linkage.
- Establish Advisory Council and Working Group/Steering Committee to develop standards on how to work with linked data (e.g., evaluate percentage unlinked, how those babies and moms differ, etc.).

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

- Conduct workshops/meetings to bring together all stakeholders to share information and develop mother/infant EHR linkage plan.
- Study systems in other countries where EHR usage was nearly universally adopted.
- Study existing US health registries

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

Steps that already have been initiated:

- AHRQ
  - State Inpatient Databases (SIDS) - as part of HCUP
  - Linking Maternal and Child Health Data to Create a Comprehensive Longitudinal Dataset. USF CPH, 2010-2013
- FDA Sentinel system
- PregSource® is an innovative NIH/NICHD project, launched in FY 2017
- CDC/NCHS Improving Health-Care Statistics Through Electronic Medical Records and Health Information Exchange
- HealthIT.gov website includes information on the types of data commonly used in EHRs
- ONC's work on EHR interoperability standards

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

Stakeholders/agencies that should be involved

- HHS agencies: ONC, CMS, CDC (NCHS), NIH, FDA, HRSA (BPHC), AHRQ, IHS
- DoD
- VA
- State agencies including State Health Departments (Maternal and Child Health (MCH) programs, etc.)
- Kaiser HMO consortium and other large health systems with EHRs
- Hospitals
- Academic: Universities (School of Medicine; School of Public Health)
- Other organizations that have EHRs

Federal agencies that should take the lead

HHS agencies :

- ONC
- CMS
- NIH (Common Funds, NICHD, NLM, another optional ICs)

Consider policy updates or new legislation

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

Potential costs

- Minimal cost to the federal government

Potential timeframes

- 2-3 years

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

Steps needed to implement this recommendation:

- Identify potential studies, databases and survey for data availability.
- Study systems in other countries. Study European systems as possible model.
- Establish a multi-organization public-private partnership initiative to develop a clearinghouse of available databases, including data dictionaries, requirements for access, associated costs, etc.
- Capture consistent data using common data elements and the presence of pregnancy and lactation information variables in large datasets.

12B. Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries (continued)

Steps that already have been initiated:

- Kaiser Permanente consortium of HMOs (Health Care System Research Network (HCSRN) that has been working to harmonize and combine data.
- AHRQ
  - State Inpatient Databases (SIDS) - as part of HCUP
  - Linking Maternal and Child Health Data to Create a Comprehensive Longitudinal Dataset. USF CPH, 2010-2013
- FDA Sentinel system
- FDA - Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP).
- NIH PregSource®

12B. Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries (continued)

Steps that already have been initiated:

- CDC case control studies provide population-based data: National Birth Defects Prevention Study (NBDPS) and Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS)
- CDC Perinatal Quality Collaboratives.
- The DoD Birth and Infant Health Registry
- Medicaid Statistical Information System (MSIS) is the primary data sources for Medicaid statistical data.
- Millennium Cohort Family Study
- VA is doing work linking state and Veterans pregnancy outcomes.
- Vital Statistics Patient Discharge Data (VSPDD)

12B. Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries (continued)

Stakeholders/agencies that should be involved

- HHS agencies: ONC, CMS, CDC (NCHS), NIH, FDA, HRSA (BPHC), AHRQ, IHS
- DoD
- VA
- State agencies including State Health Departments (Maternal and Child Health (MCH) programs, etc.)
- Kaiser HMO consortium and other large health systems with EHRs
- Hospitals
- Academic: Universities (School of Medicine; School of Public Health)
- Other organizations that have EHRs
- ACOG, SMFM, ACNM, OB-GYN practice-based networks
- Pharmaceutical industry-post marketing

Federal agencies that should take the lead

HHS agencies :

- NIH may lead in collaboration of ONC, CMS, AHRQ

12B. Leverage large studies and databases including health systems, health plans, surveillance systems, electronic medical records, registries (continued)

Potential costs

- Minimal cost to the federal government

Potential timeframes

- Identification of data sources etc. could be 4-6 months
- Specification of data elements maybe 4-6 months
- Development and determination of methodologies to analyze databases; assessment of other methods to analyze (qualitative, big data, natural language processing) - 12 months

12C. Use novel data resources

Relevant novel data sources:

- PregSource® and *All of As*/PregSource® collaboration
- US health registries:
    - The DOD Birth and Infant Health Registry
    - Millennium Cohort Family Study
- CDC case control studies
- CDC Perinatal Quality Collaboratives
- Perinatal Quality Collaboratives (federal and States) & ACOG State Quality Collaboratives Chart

12C. Use novel data resources (continued)

Steps needed to implement this recommendation:

- Reach out to the agencies/organizations that oversee these data resources.
- Obtain agreement with these agencies/organizations to share or extract chart data to conduct secondary analysis.
- Establish **large post-marketing observational studies** to evaluate the safety and effectiveness of medications during pregnancy.

None of these steps have yet been initiated

12C. Use novel data resources (continued)

Stakeholders/agencies that should be involved

- HHS agencies: ONC, CMS, CDC (NCHS), NIH, FDA, HRSA (BPHC), AHRQ, IHS
- DoD
- VA
- State agencies including State Health Departments (Maternal and Child Health (MCH) programs, etc.)
- Kaiser HMO consortium and other large health systems with EHRs
- Hospitals
- Academic: Universities (School of Medicine; School of Public Health)
- Other organizations that have EHRs
- ACOG, SMFM, ACNM, OB-GYN practice-based networks
- Pharmaceutical industry-post marketing

Federal agencies that should take the lead

- **ONC** with coordination HHS:
  - CMS
  - HRSA
  - CDC
  - AHRQ
  - NIH
  - FDA

12C. Use novel data resources (continued)

Potential costs

- Minimal cost to the federal government

Potential timeframes

- 12-18 months

12D. Use innovative methods of data analytics

- Examples of relevant, innovative methods of data analytics:
  - Probabilistic matching, unique identifiers, natural language processing.
- Contact individual experts in the field, leading academic institutions in this area, and associations focused on data analytics such as:
  - American Medical Informatics Association (AMIA)
  - American Statistical Association (ASA)
  - American Health Information Management Association (AHIMA)
  - International Society for Pharmacoepidemiology (ISPE)
  - CMS

12D. Use innovative methods of data analytics (continued)

- Use methods to link multiple data sources:
    - NIH Common Fund Program: **The Big Data to Knowledge (BD2K)** program supports the research and development of innovative and transformative approaches and tools to maximize and accelerate the utility of big data and data science in biomedical research.
    - NIH Strategic Plan for Data Science.
    - CDC Childhood Obesity Data Initiative (CODI): CODI leverages existing information technology (IT) tools in innovative ways to facilitate access to individual-level, linked, longitudinal data.

12D. Use innovative methods of data analytics (continued)

Steps are needed to use these innovative methods of data analytics

- Establish a public-private partnership to develop the strategy to utilize innovative methods of data analytics for research on pregnant women and lactating women.
- Organize workshops/meetings to bring together all stakeholders to share/exchange information and develop strategies.

None of these steps have yet been initiated

12D. Use innovative methods of data analytics (continued)

Stakeholders/agencies that should be involved

- HHS agencies: ONC, CMS, CDC (NCHS), NIH, FDA (Sentinel), HRSA , AHRQ
- AMIA
- ASA
- AHIMA
- ISPE

Federal agencies that should take the lead

HHS: CMS lead with coordination with other HHS agencies

12D. Use innovative methods of data analytics (continued)

Potential costs

- Minimal cost to the federal government

Potential timeframes

- 12-18 months

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

Steps needed to implement this recommendation:

- Survey current data elements used in potential existing data sources, studies and agencies/stakeholders
- Convene expert panel to determine common data elements (CDEs) for outcomes, to harmonize definitions for the CDEs used in obstetrics, pharmacy data, and pediatrics (pregnancy and lactation clinical features)
- Conduct research to determine feasibility for dissemination and implementation.
- Establish CDEs in pregnancy and lactation across EHRs, surveillance, research, and other data collection systems.
- Study European data as a possible model.

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

Steps that already have been initiated:

- NIH Common Data Elements (CDEs) Task Force, NLM
- NIH CDE Repository
- Use as an example:
  - NINDS Common Data Element project
  - The Accumulating Data to Optimally Predict obesity Treatment (ADOPT) Core Measures Project- comprised of interdisciplinary scientists with expertise in the behavioral, biological, environmental, and psychosocial domains
  - NIDA CTN Common Data Elements

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

Steps that already have been initiated:

- AHRQ keeps the State Inpatient Databases that allow maternal/child linkages and prospective follow-up
- ACOG led standardization efforts to harmonize definitions for the data elements used in obstetrics and gynecology
- CDC's DBDID has started to create CDE for its surveillance and research systems

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

Stakeholders/agencies that should be involved

- HHS agencies: NIH, CDC,HRSA, AHRQ
- DoD
- VA
- Private Health Plans
- Professional organizations include ACOG, SMFM, ACNM (nursing and midwifery organizations

Federal agencies that should take the lead

NIH

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

Potential costs

- Minimal cost to the federal government

Potential timeframes

- 12-18 months

Take-aways for Recommendation 12

- Establish a dedicated group of public and private agencies and stakeholders to oversee implementation of recommendations.
- Develop universal standardization and credentialing for protocols to link and harmonize data.
- Identify research gaps and develop initiatives to advance research in this area.
- Utilize available resources for data to expand the evidence base for research on pregnant and lactating women.
- Develop shareable data sources to link mother and infant data.
- Consider policy updates or new legislation to enhance implementation of goals.

Discussion