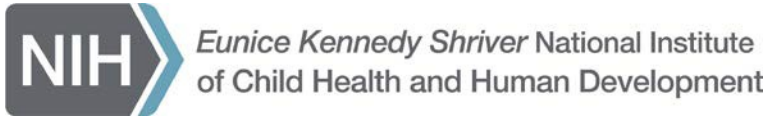
PRGLAC Working Group 1

Implementation Steps for Recommendations 2, 3, 8, and 11



Recommendation 2

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

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

What steps are needed?

- A need to educate researchers, funders, and regulators that the majority of drugs are not teratogenic.
- A need to consider what may happen if treatment to pregnant and lactating women is withheld or is not available.
  - With regulators, industry, and clinicians fearful of adverse effects on the fetus and fear of litigation, the risks currently fall on the pregnant or lactating woman.
  - Tolerance for risk must be addressed if we expect to optimize pregnancy and lactation research.

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

Potential steps by stakeholders to accomplish goals

1. Use existing resources and infrastructure to facilitate studies:

- Advocate and incentivize the CTSAs to include research in pregnant women and lactating women and develop mentorship in pregnancy- and lactation-related research.
- Explore industry-academic partnerships.
- Facilitate access to clinical research networks so that junior researchers, industry partners, and others can leverage the resources and skills of these networks.
- Collaborate with a range of partners (e.g., industry, philanthropic organizations, European agencies, etc.) to fund more research.

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

Potential steps by stakeholders to accomplish goals

2. Use existing data to inform studies in pregnancy and during lactation:

- Increase data- and specimen-sharing from networks and studies, use common data elements (CDEs), support sub-studies/ancillary studies (e.g., PK/PD studies, lactation studies) in ongoing large clinical trials.
- Leverage research results for quality improvement (QI) in health systems and incentivize centers to enroll patients and decrease research costs.
- Collaborate with researchers, EHR companies, data warehouse companies, and other purveyors of big data to add people to clinical registries by pulling data from the EHR, to identify women eligible for studies and to develop best practices for EHR-based studies.

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

Potential steps by stakeholders to accomplish goals

3. Establish new strategies to enhance research:

- Consider mechanisms to support and facilitate innovative strategies and alternative study designs (e.g., comparative effectiveness studies, multi-country trials with surrogate endpoints with their data subsequently combined into predefined meta-analyses, pragmatic trials, cluster-randomized trials, clinical trials with adaptive designs, opportunistic studies, etc.).
- Harmonize methods, common data elements (CDEs), and outcome measures across studies.
- Improve incentives for clinical staff and healthcare systems to participate in subject recruitment for studies to inform therapeutic product use in pregnant women and lactating women.
- Improve the IND process at the FDA for pregnancy-related and lactation-related research.

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

Stakeholders

- NIH, FDA, Industry.

Lead federal agency

- NIH
  - With partnership with FDA.

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

Process and costs

- An estimate of ~$25-30M annually could potentially support approximately five (5) Phase III clinical trials through existing clinical research networks.
  - An additional $3-7M could fund early phase pharmacology studies.
  - Mechanistic studies/trials would require approximately $5M annually for up to 10 projects.
- Estimated total annual costs: ~$40M.

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

Timelines

- 1-2 years: working groups could be formed.
  - Additional resources may be required to fully implement.
- 2-4 years: funding could be distributed to qualified researchers through targeted Funding Opportunity Announcements (FOAs).
  - Additional resources may be required to fully implement.
- 3-5 years: research targeting the safety and efficacy of therapeutic products used by pregnant women and lactating women could be initiated based on the grants awarded from the FOAs described above.
  - Additional resources may be required to fully implement.

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

What steps are needed?

- Specific and targeted FOAs to permit longer award periods.
  - The successes of programs that have had longer periods of funding can be used as an example of the benefits of longer award periods, especially for initiatives aimed at addressing complex and challenging clinical issues.

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

Stakeholders

- NIH.

Lead federal agency

- NIH.

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

Potential steps by stakeholders that have already taken place

- NIH supports grants that extend beyond a standard 5-year award with justification in several mechanisms; however, these types of award are still relatively rare.

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

Process and costs

- Costs associated with extending grant years would be the research costs incurred each year.
  - Based on the current grant award structure, extra costs are likely to be negligible.
- Trials conducted within clinical research networks have the advantage of taking the appropriate amount of time needed since networks are generally supported for the long-term.
  - If the clinical research networks were funded with long-term grants (>5 years), there would be no additional costs to extending the grant period for trials in networks.

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

Timelines

- 1-2 years: the establishment of priorities for long-term (>5 year) funding mechanisms.
- 2-4 years: the issuance of FOAs that would permit the funding of long-term (>5 year) awards.
- 3-5 years: research targeting the safety and efficacy of therapeutic products used by pregnant women and lactating women could be initiated based on the grants awarded from the FOAs described above.

Take-aways for Recommendation 2

- The medical and societal culture need to change in order to emphasize the importance of understanding the disease (mechanism) in pregnant women and what may happen if treatment is withheld.
  - With regulators, industry, and clinicians fearful of adverse effects on the fetus and litigation, the risk of taking medications during pregnancy and lactation for medical problems currently falls on the woman.
- There are studies currently being funded by NIH and reviewed by FDA in pregnancy and lactation research. However, few targeted efforts exist that specifically call for research in pregnant and lactating women, resulting in opportunistic studies (often with insufficient power) rather than definitive studies that can provide the evidence base to inform clinical practice and regulators.
  - What is needed is a methodical and systematic approach to funding research for pregnant and lactating women.

Recommendation 3

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

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

What steps are needed?

- A need for training health care providers and researchers in pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenomics, and pharmacoepidemiology.
  - Types of NIH training programs that could be focused on pregnancy and lactation pharmacology research include:
    - (1) Dual fellowship programs (potentially utilizing the T32 mechanism); (2) K99/R00 awards; (3) KL2/K12 awards; (4) Merit awards; (5) Diversity supplements to incorporate OBs and MFM physicians into training efforts; (6) Administrative supplements; and (7) Loan repayment programs for physicians and scientists engaged in the pregnancy and lactation pharmacology and therapeutics space.

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

What steps are needed?

- Other types of training programs that could stimulate research in this area include:
  - Clinical pharmacology certification programs to help those with clinical expertise and/or pharmacology receive training, without as large a time commitment as a traditional Master's degree or PhD training.
  - Dedicated training support within centers of excellence and existing networks aimed specifically to expand the pool of MFMs and OBs who may be interested in this field.
  - Dedicated training support within the CTSA Program aimed specifically to expand the pool of MFMs and OBs who may be interested in this field.
  - Industry partners who can offer short-term fellowship opportunities.
    - This could potentially be facilitated by cost-sharing (e.g., 50:50 salary sharing for the trainee).
  - Internships in clinical centers, networks, the FDA, and CTSAs.

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

Stakeholders

- Credentialing organizations, philanthropy, CDC, CTSAs, Medical School Deans, CMS, AHRQ, HRSA, NIH, Industry, FDA, Professional Societies (e.g., SMFM, AAP, ACOG), ACGME.

Lead federal agency

- NIH.

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

Timelines

- 1-3 years: the establishment of new training mechanisms.
- 3-5 years: the integration of obstetric and lactation pharmacology and therapeutics studies (either stand-alone or opportunistic) into clinical trial protocol development.

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

What steps are needed?

- Collaborations between academia and industry to involve industry mentors for trainees.
- Support for mentors.
- Support to help mentees identify potential mentors.
  - For example, a virtual “college of mentors” could be created in which trainees could have a mentor even if not at their own institution.
- Prioritization of training grants in this space.
- Training for mentors and trainees on FDA processes.
- Collaborations with pediatric pharmacologists
  - For example, the Research in Pediatric Developmental Pharmacology [RPDP] Network, the Pediatric Trials Network (PTN), and the CUDDLE project), particularly on studies related to medications used during pregnancy and lactation.

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

Stakeholders

- CTSAs, Medical School Deans, CMS, AHRQ, HRSA, NIH, Industry, FDA, Professional Societies, ACOG, ACGME.

Lead federal agency

- NIH.

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

Timelines

- 1-3 years: the establishment of new mentorship programs.
- 3-5 years: an increase in the pipeline of young investigators doing research in this space (due to mentorship).

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

What steps are needed?

- A need to work with accreditation bodies, credentialing groups, professional societies, board certification organizations, hospital groups, payers, professional societies, and continuing education organizations to recommend changes to requirements to help train health professionals about clinical research and pharmacology related to pregnancy and lactation.
- A need to work with continuing medical education (CME) programs, Medscape tutorials, and Maintenance of Certification (MOC) Programs for Allied Health Professionals (e.g., nurses, midwives, lactation consultants, and pharmacists) and physicians (e.g., MFMs, OBs, and pediatricians) to increase awareness.
- A need to create incentives by providing easy, online training opportunities.

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

Stakeholders

- CTSAs, Medical School Deans, CMS, AHRQ, HRSA, NIH, Industry, FDA, Professional Societies (e.g., SMFM, AAP, ACOG), ACGME.

Lead federal agency

- NIH?

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

Potential steps by stakeholders that have already taken place

- Some electronic medical record (EMR) modules exist that help healthcare providers identify eligible patients for clinical trials.
    - These could be expanded to identify women who are pregnant and/or lactating.

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

Timelines

- 1-3 years: the creation of new programs to engage health care providers in this space.
- 3-5 years: the integration of new programs into accreditation and/or credentialing systems.

Take-aways for Recommendation 3

What steps are needed?

- Increase support for research in obstetric and lactation pharmacology and therapeutics.
  - Additional resources may be required to fully implement.
- Invest in the training of health care providers in obstetric and lactation pharmacology and therapeutics through training programs, collaborations, internships, etc.
- Invest in mentors to provide the training through grants, supplements, etc.
- Increase public-private partnerships to facilitate research endeavors in this space.
- Engage accreditation bodies, credentialing groups, professional societies, payers, funders, and CE organizations so clinicians and research investigators are incentivized to do research in this space.
- Invest to expand the scope of relevant networks to incorporate research in obstetric and lactation pharmacology and therapeutics into their mission.
  - Additional resources may be required to fully implement.

Recommendation 8

Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the NIH BPCA model

8A. Provide specific funding

What steps are needed?

- A need to establish an infrastructure to conduct research in off-patent drugs and supplements in pregnant women and lactating women.
  - Additional resources my be required to fully implement.
- A need to establish a prioritization of drugs based on experience with BPCA and the Pediatric Research Equity Act (PREA).
- A need to coordinate drug testing along the continuum from pregnancy through lactation/ breastfeeding.
  - It is important that the pregnancy and lactation research be paired together.

8A. Provide specific funding

What steps are needed?

- A need to leverage existing data to design studies, simulate doses, and inform FDA's review process.
- A need to support technology development that would substitute for human trials or that could truncate research in humans.
- A need to support shared cost efforts of generic manufacturers to join a pregnancy registry to obtain more data.
- A need to incentivize clinical providers to contribute data to registries.

8A. Provide specific funding

Stakeholders

- NIH, FDA, academic researchers, professional societies (e.g., SMFM, ACOG, AAP).

Lead federal agency

- NIH.

8A. Provide specific funding

Process and costs

- An estimate of ~$12M per year for pregnancy research.
- An estimate of ~$4M per year for lactation research.

8A. Provide specific funding

Timelines

- 1-3 years: the NICHD-supported OPRCs and MFMU Network are already in existence; a BPCA-like program could potentially be established rather quickly.
  - Additional resources may be required to fully implement.
- 3-5 years: new clinical trials studying therapeutic products used off-patent in pregnant and lactating women could be launched.

8A. Provide specific funding

Existing programs to address recommendation

- The NICHD-supported OPRCs and MFMU Network are already in existence; a BPCA-like program could potentially be established rather quickly.
  - Additional resources may be required to fully implement.

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

What steps are needed?

- A need to establish separate prioritization processes and programs for testing therapies and/or conditions in pregnant women and lactating women.
  - In consideration of the current maternal morbidity and mortality (MMM) crisis, this effort could also dovetail with other strategies to reduce MMM.
    - Novel therapies and evidence of their safety and efficacy in pregnant women may augment efforts to prevent or reduce MMM.
  - Additional resources may be required to fully implement.

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

Stakeholders

- NIH, FDA, academic researchers, professional societies (e.g., SMFM, ACOG, AAP).

Lead federal agency

- NIH.

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

Timelines

- 1-3 years: the NICHD-supported OPRCs and MFMU Network are already in existence; a BPCA-like program could potentially be established rather quickly.
  - Additional resources may be required to fully implement.
- 3-5 years: new clinical trials studying therapeutic products used off-patent in pregnant and lactating women could be launched.

Take-aways for Recommendation 8

What steps are needed?

- Establish an infrastructure to conduct research and study therapeutic products used off-patent in pregnant women and lactating women.
  - Additional resources may be required to fully implement.
- Establish separate prioritization processes for therapies and/or conditions in pregnant women and lactating women.
  - Additional resources may be required to fully implement.

Recommendation 11

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

11A. Provide financial support and incentives to established and develop new multicenter infrastructures that capitalize on standard of care procedures (opportunistic studies), innovative designs, and methodologies

What steps are needed?

- A need to support the infrastructure of clinical trial networks and add more enrolling sites from diverse areas to broaden the participant pool of pregnant and lactating women.
  - Additional resources may be required in order to:
    - Support investigators, who are largely clinicians, to have ample time to devote to research.
    - Support the long-term follow-up studies that are unique to pregnancy and lactation research to ascertain safety outcomes for specific medications on the offspring.

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

What steps are needed?

- A need to encourage investigator-initiated projects that test products in pregnant and lactating women.
  - Which could be conducted within an appropriate Network (e.g., MFMU Network).
- A need to consider the creation a new network model specifically for the testing of products used during pregnancy and lactation.
  - A model to consider is the Pediatric Trials Network (PTN) in which sites cooperate in the design and conduct of trials to provide evidence for optimal dosing of commonly used medications in infants and children.

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

What steps are needed?

- A need to encourage and develop streamlined processes for collaborations among industry, philanthropy, and government as an important strategy to support clinical research.
  - A novel partnership is the Innovative Medicines Initiative (IMI) in Europe which is funded equally by industry and the EU to conduct health research and innovation – the partnership has 144 funded projects (https://www.imi.europa.eu/).
    - Something similar in the US could facilitate product testing and also address the stigma that can affect academic researchers in the U.S. who collaborate with the pharmaceutical industry.

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

Stakeholders

- Governmental as well as non-governmental entities.
    - A trans-NIH coordinating committee or similar structure might help facilitate the exchange of expertise among researchers new to pregnancy and lactation research with those who have expertise in pharmacology and in specific conditions that affect pregnant women.

Lead federal agency

- NIH should lead on the research aspects.
- FDA should lead on the regulatory aspects.

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

Potential steps by stakeholders that have already taken place

- Networks/collaborations currently exist that are conducting studies and trials in pregnant and less commonly, lactating women.
  - The NICHD MFMU Network conducts studies and trials in pregnant women and has completed efficacy trials testing aspirin, antibiotics, tocolytics, antioxidants, and several other agents.
  - The NICHD's Obstetric-Fetal Pharmacology Research Centers (OPRCs) are the nexus for early phase studies having tested agents such as thyroxin, antiemetics, antibiotics, progestins, antidiabetics, statins, and more.

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

Process and costs

- Encourage investigator-initiated projects that test products in pregnant and lactating women that are conducted within an appropriate Network.
  - A model such as the Pediatric Trials Network (PTN) receives $11-12M per year of BPCA funds and is able to execute 1-2 studies annually focused largely on PK studies. In 2018, the Network enrolled 1523 subjects at 130 active sites. Some studies evaluate multiple drugs and use opportunistic approaches.
- Encourage and develop streamlined processes for collaborations among industry, philanthropy, and government as an important strategy to support clinical research.

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

Timelines

- 1-2 years: studies that focus on drugs that are currently being used off label could begin within existing networks.
- 2-4 years: scaling up new infrastructure, developing partnerships, and other efforts would take several years.
- 3-5 years: the ability to more efficiently and effectively perform studies that focus on drugs that are currently being used off label in pregnancy and lactation would increase due to novel partnerships, networks, and collaborations.

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

What steps are needed?

- A need to develop a platform to share expertise.
- A need to establish relationships with industry to partner in product testing.
- A need to enrich existing Networks with pharmacology expertise.
- A need for investigators to work with the FDA to establish standards for assessing risk in pregnancy and lactation research and to establish appropriate endpoints and identify factors (i.e., drug-related or disease-related) that would require long-term follow-up of offspring.
- A need to identify and agree on the relevance of timelines and the appropriateness of endpoints recommended for long-term follow-up of infants.
- A need to identify high unmet need areas within the pregnancy and lactation space and those that do not have active registries/networks in place (e.g., the area of inflammatory diseases [e.g., RA, IBD, etc.]) in order to hone next steps and maximize impact.

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

Stakeholders

- Other stakeholders beyond NIH include industry, FDA, CDC, and others.

Lead federal agency

- NIH should lead on the research aspects.
- FDA should lead on the regulatory aspects.

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

What steps are needed?

- Public private partnerships need to be developed very carefully.
  - Clear objectives need to be agreed upon at the outset as each partner may have a different goal (e.g., industry wants to evaluate a product, foundations may want good publicity, researchers want treatments for patients, the FDA wants sufficient safety and dosing data, etc.). It is important to create a win-win for each partner for success.
- These partnerships can often leverage existing infrastructure or clinical trial networks (in either the public or private space) to enhance efficiency.
- Another model is a consortium of public-private partnerships where multiple industry partners work with a research network (or multiple networks) to study product safety in one or more therapeutic areas.

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

Timelines

- Public private partnerships require considerable time, effort, and thought to develop.
  - Clearly defining roles and responsibilities, and addressing issues like data sharing, liability, and operating procedures must come before research can be done.
- Simple partnerships between one Network and an industry partner may take little time to establish, but establishing a partnership such as the EU IMI would take considerable time and effort.

Take-aways for Recommendation 11

What steps are needed?

- Support networks that perform studies in pregnant and lactating women.
  - Additional resources may be required to fully implement.
- Incentivize investigator-initiated research that tests products in pregnant and lactating women.
- Facilitate access of investigators to clinical trial networks with the requisite expertise to perform research in pregnant and lactating women.
- Streamline processes for collaborations and public-private partnerships among industry, philanthropy, and government for research in this space.
- Improve the use and usability of current registries.

Take-aways for Recommendation 11

Lead federal agencies

- NIH should lead on the research aspects.
- FDA should lead on the regulatory aspects.

Potential costs

- An estimate of ~$40M per year to current funding levels for research networks and infrastructure.
- An estimate of an additional ~$10M per year to current funding levels for early phase pharmacology studies that would form the basis for the efficacy trials.
- Other costs to be determined.

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Discussion