NATIONAL ACADEMIES Sciences Engineering Medicine

Advancing Clinical Research with Pregnant and Lactating Populations

Overcoming Real and Perceived Liability Risks

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Background

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The Benefits and Risks of Research

- Pregnant and lactating women are excluded from clinical studies that evaluate medications and vaccines
- Clinical research is a benefit to society
- Research generates evidence leading to discoveries and innovation
- Research is a means to improve health equity
- Participation in research generally involves some exposure to risks
- Research protections exist to identify, minimize, and explain those risks

Statement of Task

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Statement of Task

- Conduct a study on the state of real and perceived liability around research conducted in pregnant and lactating persons which lays out a framework for addressing medicolegal and liability issues when planning or conducting research specific to pregnant and lactating persons.
- Conduct data collection and analysis of the state laws governing liability for conducting research
- Develop a report with findings, conclusions, and recommendations for safely and ethically including pregnant and lactating persons in clinical research that substantially mitigates or avoids incurring liability.

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Legal Liability

03

Harm and Liability

- There are many forms that harm can take
  - Injury resulting from clinical research participation
  - Harms of exclusion from clinical research
- Harm is required to occur for there to be liability, ***but*** not all harms will lead to a finding of liability
- Reducing harm reduces potential for liability

Defining Liability

- Liability has a precise definition in the legal field
- Legal liability refers to responsibility for harm experienced by an individual due to the actions or inactions of another
- To better understand the scope of liability considerations, the committee evaluated legal liability risks

Liability for Pregnant Women

- No reported cases for investigational medical product use in pregnant women after 1962 regulation changes
- Over 1000 filed cases associated with pregnant women's postmarket use of medical products
- Little liability in the clinical research setting, but there is evidence of liability once products are on the market
  - Some of this liability may be obviated by inclusion of pregnant women in clinical studies

Liability for Lactating Women

- No reported cases for investigational medical product use in lactating women
- No cases involving injury to a child caused by use of a medical product by a lactating woman in the postmarket setting
- All reported postmarket cases were for a lactation inhibitor and involved injury to the mother
- Limited liability for lactating women in both the research and postmarket settings

Because evidence does not indicate that liability is a concern for conducting research with lactating women, examining the challenges of including both pregnant and lactating women in clinical research as a single group conflates the unique challenges in each population.

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CONCLUSION 2-1

Perceptions of Liability

- Fear of liability seems to exist in uncertainty
- Potential harms involve a fetus who cannot consent likely worsens uncertainty
- Long shadow of thalidomide and DES
- Focusing on liability risks makes it easier to focus on risks for inclusion, while ignoring risks associated with not conducting research with pregnant and lactating women

The lack of evidence of liability for including pregnant and lactating women in clinical research suggests that liability is not the sole factor that dissuades sponsors, research institutions, investigators, and IRBs from including pregnant and lactating women in clinical research.

CONCLUSION 2-2

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Minimize Harm

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Strategies to Reduce Harm –Postmarket Safety Monitoring

- Most safety data for pregnant and lactating women is through postmarketing observational studies
- Critical for observing long-term safety and detecting rare events
- Better integration, more information and accessibility, and a way to link mother-child health records would improve current system

The U.S. Department of Health and Human Services should form an interagency task force, including the Food and Drug Administration, National Institutes of Health, Centers for Disease Control and Prevention, Health Resources and Services Administration, Office of the National Coordinator for Health Information Technology, and the National Library of Medicine to create and maintain infrastructure and guidelines for the conduct of postmarketing pregnancy and lactation safety studies that would use safety information, annual status reports from existing pregnancy and lactation exposure registries, and data generated through database studies.

RECOMMENDATION 8

Strategies to Reduce Harm – Federal Protections for Human Subjects

- HHS regulations for the protection of human subjects in research
  - Subpart B provides additional protections for pregnant women, human fetuses and neonates
    - Unclear definitions of “risk” and “benefit”
    - No guidance for interpreting “minimal risk” standard
  - Subpart D provides additional protections for children
    - Unclear if it applies when a child is exposed to the milk of a lactating woman participating in research

The Office for Human Research Protections (OHRP) within the U.S. Department of Health and Human Services should provide clarity on the inclusion of pregnant and lactating women as research subjects. OHRP should provide guidance documents that help clinical researchers, institutional review boards (IRBs), and data and safety monitoring boards ensure that pregnant and lactating women who participate in clinical research are adequately protected without creating undue burdens for their participation. OHRP should work with the Food and Drug Administration (FDA) to harmonize applicable guidance pertinent to research with pregnant and lactating women.

RECOMMENDATION 3

Strategies to Reduce Harm – FDA Guidance

- Strengthen FDA guidance for research involving both pregnant and lactating women
  - Set timelines for completion
  - Provide details on follow-up examination required
  - Information on what FDA considers sufficient evidence to evaluate safety of medical products

The U.S. Food and Drug Administration (FDA) should revise guidance to make clear its expectation that pregnant and lactating women should be included as early as possible in the studies conducted for product approval of medical products that pregnant and lactating women are expected to use, and that studies to provide explicit support for the safety, efficacy, and dosage in these populations be initiated no later than the end of Phase III studies in the general population. The studies with pregnant and lactating women should continue into the postapproval period and be completed as quickly as possible postapproval. FDA should bring all related guidance documents into conformity with the revised guidance.

RECOMMENDATION 1

Mitigating Liability

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Mitigating Liability - Stakeholders

- Industry sponsors
- Research institutions
- IRBs
- Investigators
- Pregnant research participants

Mitigating Liability for Sponsors, Research Institutions, and Investigators

- Informed consent
- No-fault administrative compensation systems
- Tort reform
- Clinical trial insurance

The National Institutes of Health (NIH) and other federal agencies that fund clinical research should cover the cost of clinical trial insurance on clinical trial grants that include pregnant and lactating women for research that is conducted domestically. The additional expense of this insurance should be deemed as outside of the NIH cap for direct costs for grant awards.

RECOMMENDATION 7

Mitigating Criminal and Civil Liability for Pregnant Research Participants

- Shifting legal landscape following *Dobbs v. Jackson Women's Health Organization*
- Protecting privacy more important than ever
- Criminal and civil liability will likely increase in certain states willing to interpret pregnant women's participation in research as risky behavior that could affect her fetus

If research being conducted with pregnant individuals, or individuals who may become pregnant over the course of the study, is not already covered by a certificate of confidentiality issued by the National Institutes of Health or other federal agency, the principal investigator of the study should apply to the National Institutes of Health for a certificate of confidentiality.

RECOMMENDATION 9

Dissuasive and Persuasive Factors

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A CULTURE OF EXCLUSION

systematic underfunding of women's health research

CHALLENGES WITH RECRUITMENT AND ENROLLMENT

inadequate resources for investigators and research participants to recruit or enroll in studies

LACK OF RESEARCH EXPERTISE

limited number of trained investigators with expertise conducting research with pregnant and lactating women

REPUTATIONAL RISK

concerns for negative publicity

COST AND COMPLEXITY

unwillingness to invest time and resources to properly conduct studies with pregnant and lactating women

LACK OF FINANCIAL INCENTIVES

insufficient financial return on investment for additional research

Persuasive Factors – On-Market, Off-Patent Products

- Sponsor has no financial incentive to conduct research once off-patent
- NIH investment needed
- Similarities to challenges in research with pediatric populations
  - Best Pharmaceuticals for Children Act (BPCA)

The National Institutes of Health (NIH) should develop an action plan to prioritize research that includes pregnant and lactating women across its institutes and centers. At a minimum, the action plan should include the following:

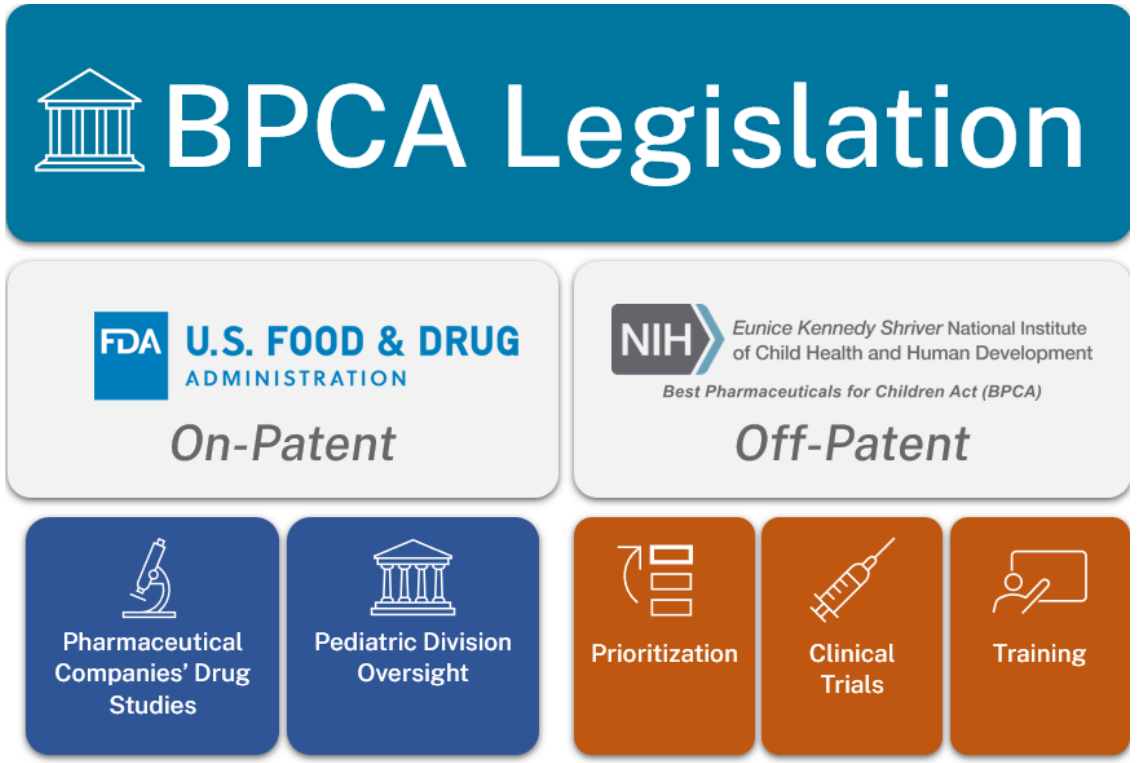
a. NIH should create a new program with the NIH Common Fund to study the pharmacokinetics, pharmacodynamics, and dosage determination of on-market drugs in pregnant and lactating women.

b. The Eunice Kennedy Shriver National Institute of Child Health and Human Development should expand and sustain its network of institutions with expertise in conducting clinical research with pregnant and lactating women, with considerations for the equitable access of potential research participants.

RECOMMENDATION 6

Persuasive Factors – On-Market, On-Patent Products

- Sponsor has little financial incentive to conduct additional research once product is on-market
- Provide incentives to sponsors
  - BPCA is a useful model



The U.S. Congress should pass legislation modeled on the Best Pharmaceuticals for Children Act to encourage and incentivize additional studies to provide more information in labeling on the safety and efficacy of approved medical products for pregnant and lactating women.

RECOMMENDATION 4

Persuasive Factors –Products in Development

- FDA does not have authority to mandate studies be conducted in pregnant and lactating women
- Legal requirement
  - Pediatric Research Equity Act (PREA)

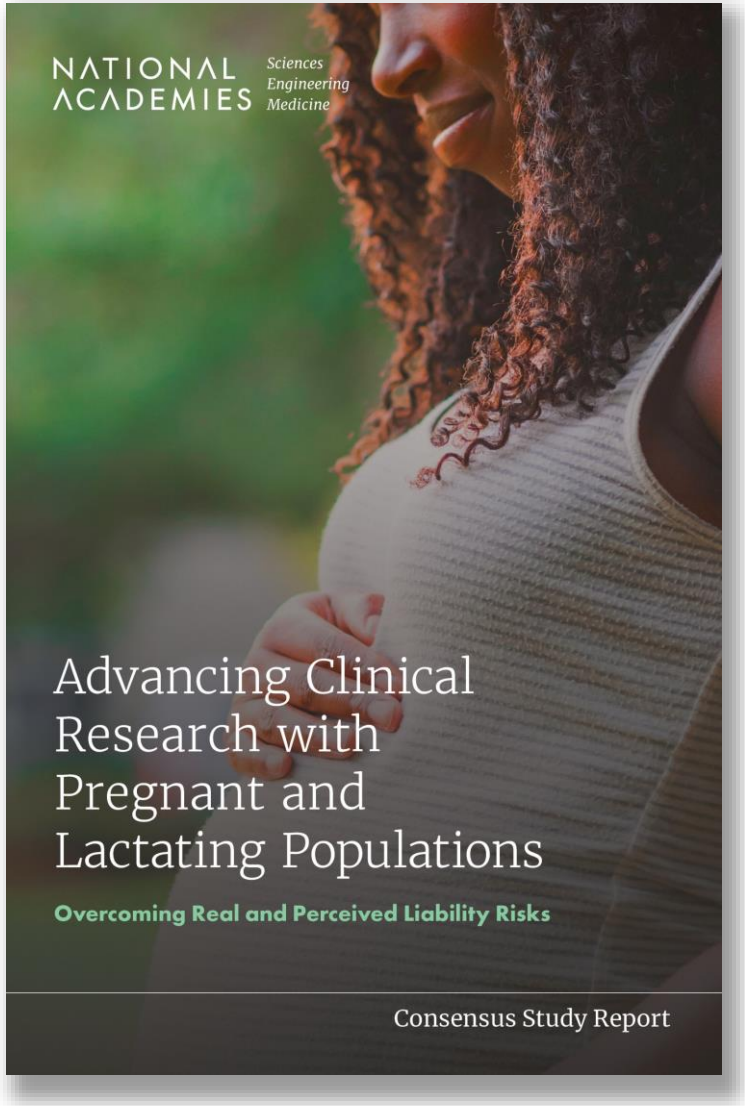
The U.S. Congress should pass legislation modeled on the Pediatric Research Equity Act to authorize the Food and Drug Administration (FDA) to require research related to the use of drugs, biologics, vaccines, and medical devices in pregnant and lactating women.

RECOMMENDATION 5

Thank You for Listening

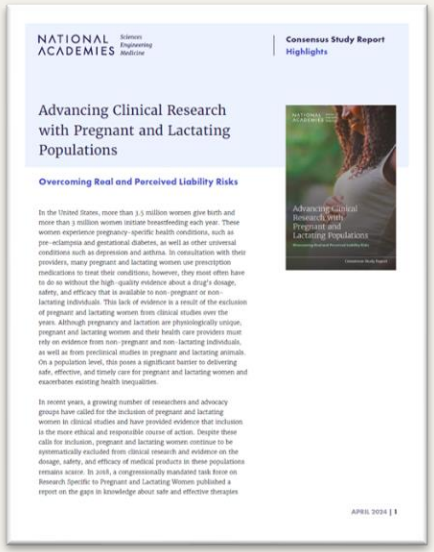
The full report is available for free download at the QR code below

nationalacademies.org/liability-study



Additional Resources

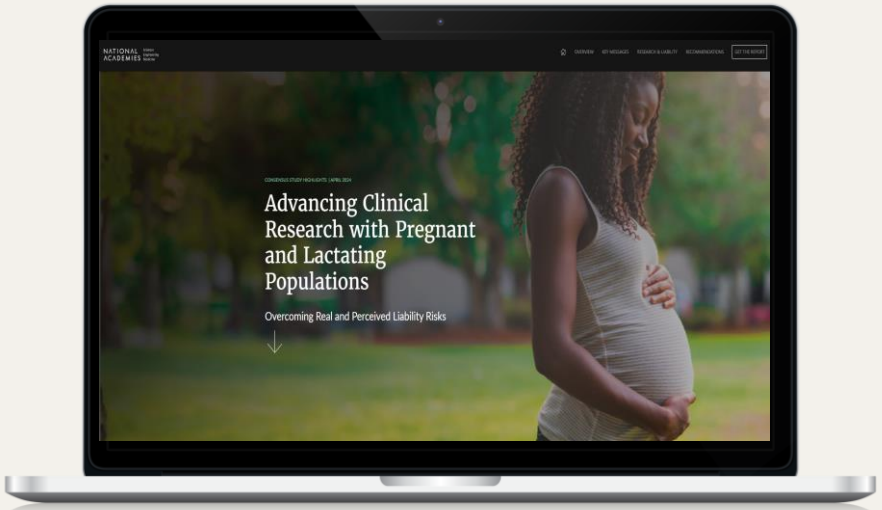
Highlights



Policy Briefs

Video

Interactive Page



Questions?

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