

# Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks

## Role of the Food and Drug Administration

Congress requested that a committee of the National Academies of Sciences, Engineering, and Medicine undertake a comprehensive overview of the real and perceived liability around research conducted with pregnant and lactating women. This included a review of the legal landscape of tort liability for injuries related to pregnant and lactating populations' participation in clinical trials and use of products regulated by the Food and Drug Administration (FDA).

The committee found limited liability risk related to the use of medical products in clinical trials for both pregnant and lactating populations. The committee found evidence of potential liability relating to pregnant women's use of approved medical products on the market and that aspects of this liability may be prevented by conducting clinical trials with pregnant women. Despite this, perceptions and fear of liability remain.

Action is needed from federal agencies, including FDA, to improve the responsible and ethical inclusion of pregnant and lactating women in clinical research while mitigating the risk of legal liability. As the federal agency tasked with regulating medical products, FDA has a responsibility to require preclinical and clinical studies to demonstrate that the product has a favorable benefit-risk balance for use in its intended population prior to

FDA approval. Despite these requirements, pregnant and lactating women often must use FDA-approved products for on-label indications without accompanying safety, efficacy, and dosage data tailored to pregnant and lactating populations. To remedy this situation, specific report recommendations for FDA are listed below.

### RECOMMENDATIONS

**FDA should revise guidance to make clear its expectation that pregnant and lactating women should be included as early as possible in studies and that studies on the safety, efficacy, and dosage in these populations be initiated no later than the end of Phase III studies in the general population.**

Clear guidance from FDA can provide a pathway for critical stakeholders directly engaged in clinical research to enhance the conduct of research with pregnant and lactating women that minimizes the anticipated risk of harm. By minimizing potential harm, this guidance also mitigates potential liability associated with that harm. Regulatory clarity and consistency are paramount to reducing medical product sponsors' uncertainty in regulatory expectations and may influence decisions to pursue any type of research, including studies involving pregnant and lactating women.

The avoidance of clinical research with pregnant and lactating women has resulted in insufficient evidence on the safety, efficacy, and dosage of the medical products being used by pregnant and lactating women. FDA guidance on how to appropriately conduct studies with these populations, including the timing of studies, would help sponsors understand and account for the expected practices that can minimize harm. FDA guidance on the appropriate conduct of real-world evidence studies and other observational research would also help improve sponsors' understanding of FDA expectations.

**FDA should use the authority outlined in Public Law 117-328 to require that diversity action plans include pregnant and lactating women as part of an intersectional plan to increase the inclusion of diverse populations in clinical research.**

The Food and Drug Omnibus Reform Act (FDORA) gave FDA the authority to require diversity action plans from sponsors, which are intended to detail the sponsor's diversity goals and strategies for achieving the identified goals. FDORA also requires FDA to develop guidance on the content and format of diversity action plans and includes pregnant and lactating women as groups that may be relevant to include in the plans. Including pregnant and lactating women as categories in diversity action plans would ensure sponsors consider these populations at the beginning of the clinical development process.

Conversations between sponsors and FDA regarding plans to include pregnant and lactating women in clinical studies would also promote information exchange about appropriate study designs and safeguards. Requiring early consideration for the safe inclusion of pregnant and lactating women may reduce the potential for legal liability by promoting intentional and thoughtful planning that aims to reduce harm to study participants.

**FDA should work with the U.S. Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) to harmonize applicable guidance pertinent to research with pregnant and lactating women.**

FDA has its own regulations for the protection of human subjects and institutional review boards (IRBs) and has not adopted the regulations used by HHS. FDA's regulations for human subject protections and IRBs do not have specific considerations for pregnancy, other than to note that IRBs are to implement additional safeguards for clinical studies that include pregnant women and that IRBs might consider including individuals with relevant expertise among their membership if they regularly review protocols that include pregnant women.

The committee calls for OHRP to provide guidance documents that help stakeholders, such as IRBs, ensure that pregnant and lactating women who participate in clinical research are adequately protected without creating undue burdens for their participation. FDA should work with OHRP to harmonize guidance so that investigators and their institutions are following uniform guidelines and language for research involving pregnant and lactating women.

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

Under the PREA, FDA can require drug sponsors to conduct studies and clinical trials to evaluate safety, efficacy, and dosage in pediatric populations when a drug is deemed "relevant" to children. FDA authority could be expanded to enforce the same requirements to conduct clinical studies for pregnant and lactating women.

Because pregnant and lactating women are rarely studied as part of premarket review, many risks these populations are unknown when the drug enters the market. Like pediatric populations before the PREA was enacted, this leaves pregnant and lactating women unprotected and uninformed until signals are detected through postmarketing surveillance. This amounts to experimenting on pregnant and lactating women at the population level.

The committee also recommends Congress amend the Food, Drug, and Cosmetic Act to expand FDA's authority to require postmarketing studies and postmarketing clinical trials, as well as create programs such as extended market exclusivity or tax breaks to ease the initial challenges that may be faced in implementing this requirement.

**HHS should form an interagency task force, including FDA, 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 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.**

Real-world data collected through observational studies are important for detecting rare adverse events and understanding the long-term safety profile of medical products. However, the current system of real-world

data capture and analysis needs substantial improvement before it can play a major role in increasing knowledge about the effects of medical products in pregnant and lactating women.

Although FDA maintains a list of pregnancy exposure registries on its website, that list has limited search capabilities and is not complete. Registries are listed only at the request of the registry sponsor or investigator. A central repository of interoperable pregnancy exposure registries could facilitate enrollment by making registries more accessible for pregnant individuals, clinicians, and researchers. Including the results of complementary database studies in the central repository would also be a useful mechanism to provide stakeholders with information regarding the safety of medical products during pregnancy and lactation. An important first step in designing such a repository would be to make it an interoperable, searchable resource for clinicians, investigators, or potential participants. Including additional information, such as adverse event data captured by the FDA Adverse Event Reporting System and Vaccine Adverse Event Reporting System, in one centralized location would be helpful.

#### FOR MORE INFORMATION

To access the full report, visit [nationalacademies.org/liability-study](https://www.nationalacademies.org/liability-study).

#### Health and Medicine Division

