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National Academies of Science, Engineering, and Medicine Issues Report on Inclusion of Pregnant and Lactating Persons in Clinical Research

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In April 2024, the National Academies of Science, Engineering, and Medicine ("NASEM") issued a **report** discussing the inclusion of pregnant and lactating people in clinical research and the health impacts of inadequate data from research involving this subpopulation. Titled "Advancing Clinical Research with Pregnant and Lactating Persons: Overcoming Real and Perceived Liability Risks," the report came as a response to Congress calling upon NASEM to examine the real and perceived prevalence of legal liability resulting from including these research subjects in clinical trials. Overall, the report concluded that legal liability for including pregnant and lactating persons in research is very limited, but that perceptions of potential liability and a lack of explicit guidance for including this population safely have created real barriers to their inclusion. In response, the report provides recommended actions for Congress, the Food and Drug Administration ("FDA"), the National Institutes of Health ("NIH"), and the Office of Human Research Protections ("OHRP") to take to enhance the inclusion of this population in clinical trials, thereby enhancing data around the safety and efficacy of approved drug products for pregnant and lactating persons. Study sponsors and institutions conducting research should continue to monitor developments in this area, including guidance from FDA.

Background

Following the approval of a drug and its introduction to the market, inadequate data from pregnant and lactating research participants can lead to a variety of health risks. First, providers are left to prescribe medications without having adequate data about dosage, efficacy, and safety for this unique population. Second, some pregnant or lactating individuals choose to forego medication due to uncertainty of the medication's impact on the fetus or the nursing child. NASEM notes that this is of heightened importance given that 70% of pregnant persons and at least 50% of lactating persons take medications, many for chronic conditions. Without adequate pregnancy or lactation data available in controlled clinical studies, patients and their providers are often left to individually assess the clinical benefit and risk associated with any particular medication.

The report's authors were charged with evaluating the risk of legal liability for sponsors when pregnant and lactating persons are included in clinical trials. In doing so, the authors argue that risk of legal liability is greater when excluding pregnant and lactating persons in research compared to including the population with protective safety measures. The historical exclusion of pregnant and lactating patients has, in effect, led to these patients taking medications for which there is insufficient safety and efficacy evidence. According to the report, if this population were safely included in clinical studies, legal and health risks would diminish because the impacts of medications could be measured within a small study population. This realization gave rise to Congress authorizing the creation of a Task Force on Research Specific to Pregnant and Lactating Women (the "PRGLAC") in 2016 to evaluate gaps in knowledge regarding safe and effective therapies for this population. The PRGLAC released a report in 2018, revealing that possibility and fear of legal liability is often a root cause of excluding pregnant and lactating women in clinical research.

Report Findings on Liability

The report includes a review of case law to determine (i) the prevalence of liability cases stemming from harm to pregnant and lactating research participants and (ii) the harm to pregnant and lactating patients who take a drug after it has been approved. Generally, the report found there were no legal liability claims from the involvement of pregnant and lactating persons in clinical trials for pre-market medications since 1962, the year the Food and Drug Administration (FDA) was granted authority to require proof of safety and efficacy of products before going to market. However, the report indicated

there have been numerous cases arising from the use of post-market drugs by pregnant and lactating patients. We believe these findings may be somewhat limited. Given most clinical studies categorically exclude pregnant and lactating individuals, the number of potential claims able to be filed is very low.

Report Recommendations

The report provides nine recommendations for addressing the inclusion of pregnant and lactating persons in clinical research. We provide a summary of NASEM's recommendations, specifically highlighting those we find most realistic and effective, below.

1. FDA Regulations and Guidance

The report proposes that FDA revise guidance to set forth its expectation that pregnant and lactating persons be included early in studies, no later than the end of Phase III, for products expected to be used by these populations following approval. Among other things, the report proposes that FDA provide study designs, safeguards, and product-specific monitoring expected for conducting studies with this population. Such standards may help to minimize potential harm to research participants and thereby reduce the potential for liability from adverse outcomes.

Additionally, the report calls on FDA to require the inclusion of pregnant and lactating persons in diversity action plans when a drug is anticipated to be used in this population. Our FDA colleagues have previously covered diversity action plans **in a previous post**. The regulated community eagerly awaits further guidance from FDA on the issue.

2. OHRP Guidance

The report suggests that OHRP issue clarifying guidance targeted at clinical researchers, institutional review boards, and data and safety monitoring boards. Specifically, the authors recommend guidance on the definitions of "minimal risk" and "additional safeguards" in existing regulations governing additional protections for pregnant women, fetuses, and neonates in research. Additionally, they propose guidance include frequently asked questions to assist researchers in assessing risk and justifications for inclusion of pregnant and lactating research subjects. As the authors acknowledge, harmonizing OHRP and FDA guidance on the standards for review by IRBs will be critical in ensuring that the regulated community has a consistent set of standards and guidance to follow.

3. Federal Legislation

The report calls upon Congress to pass new legislation to incentivize manufacturers to include pregnant and lactating participants in research. In doing so, the authors believe any proposed legislation should be modeled on the **Best Pharmaceuticals for Children Act** and the **Pediatric Research Equity Act**. To address the lack of incentivization by manufacturers to conduct studies in these populations, legislation could offer manufacturers extended market or data exclusivity, as well as tax breaks. Finally, the authors propose Congress enact legislation granting FDA the authority to require research related to the use of drugs, biologics, vaccines, and devices in pregnant and lactating women.

4. Action from NIH

Separate from incentives for manufacturers, the report calls upon the NIH to prioritize research that includes this subpopulation, developing priority lists of approved medicinal products that stand to benefit most from further research. Moreover, the authors encourage the NIH and other federal agencies cover the cost of clinical trial insurance for federally funded studies that include pregnant and lactating persons in the trial population, suggesting that the additional expense should not be included in the NIH cap for direct costs for grant awards. Covering the expense of clinical trial insurance could both increase the willingness of institutions to conduct research in this population, without significant financial risk to the institution, and address ethical concerns around the availability of compensation for research harms and the equitable provision of that compensation.

5. Protecting privacy through certificates of confidentiality

Lastly, the report proposes researchers utilize **certificates of confidentiality** to provide greater privacy protections for this population's research data. In the aftermath of the Dobbs v. Jackson Women's Health decision and the continued passage of restrictive abortion laws at the state level, **researchers have raised** a number of concerns regarding the collection of pregnancy-related information from research subjects. **Certificates of confidentiality** issued by NIH prohibit identifiable, sensitive research information from being accessed to anyone outside of the research study. While certificates of confidentiality are automatically granted for federally funded research, researchers conducting studies with non-federal funding sources can also apply to the NIH for a certificate.

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