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Advancing Clinical Research with Pregnant and Lactating Populations

Overcoming Real and Perceived Liability Risks

Margaret Foster Riley, Alex Helman, and Andrew March, *Editors*

Committee on Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons

Board on Health Sciences Policy

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Consensus Study Report

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This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **BRUCE N. CALONGE,** University of Colorado School of Medicine, and **ELLEN W. CLAYTON,** Vanderbilt University Medical Center. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

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Preface

My three children were born between 1990 and 2000. I was extremely fortunate that my overall health was good and that I had few health issues during my pregnancies and later when nursing my children. Even as a healthy pregnant and lactating woman, I had so many questions for my doctors. I wanted to know how certain medications might affect me or my fetus and later my infant. I was frustrated when my doctors could not answer my questions with confidence. I worried.

Between the time my first child was born in 1990 and the third was born in 2000, the clinical research landscape changed dramatically. In 1990, most research participants in the United States were White men. By 2000, the human subjects research laws and regulations were changed to encourage the participation of women, including women of childbearing potential, and efforts had been made to improve the ethnic diversity of research participants. Soon after, legislation was passed to promote clinical research with pediatric populations to study medications that were used by children. There is still much work to be done to improve the diversity of our research populations, but as a society, we have made progress gathering and acknowledging the value of collecting evidence about how medical treatments may affect women, children, and people of different races and ethnicities.

One thing has not changed: there is still a dearth of data about the appropriate dosage, efficacy, and safety of most medical interventions used by pregnant and lactating women. This stood out during our experience with the COVID-19 pandemic. Despite broad liability protections for

medical product manufacturers, health care providers, and others, pregnant and lactating women were not included in the preauthorization clinical trials for vaccines. Although their exclusion from research has since been remedied, for months these populations were without evidence of their safety and efficacy and ultimately reducing vaccine uptake in these populations. If my daughter were to become pregnant now, she would likely have the same kind of unanswered questions for her doctors that I had when I was pregnant with her.

Despite a national and international consensus that avoiding research involving pregnant and lactating women is causing real harm, concerns about potential liability continue to thwart efforts to expand that research. No one has deeply studied the assumptions and realities behind those concerns about liability. This committee has done a thorough examination of the forces—legal, financial, and cultural—that disincentivize research with pregnant and lactating women. The committee provides evidence that conducting clinical studies with pregnant and lactating populations is not currently fraught with liability and how such research can—and must—be done safely and well.

Our committee is indebted to the work of the U.S. Department of Health and Human Services Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC Task Force), which provided foundational knowledge for this committee to build from and which recommended that such a committee as ours be established. I am also grateful to the many experts who shared their knowledge of the complex legal and clinical landscapes in our public meetings and to the outstanding people who created our four commissioned papers. I am particularly grateful to the National Academies of Sciences, Engineering, and Medicine staff, led by Alex Helman and Andrew March, who provided guidance and expertise as well as thousands of hours of supporting research and editing.

Finally, I am grateful to have worked with an amazing group of committed experts on this consensus committee, many of whom have devoted their entire careers to improving health for pregnant and lactating women. Everyone generously volunteered countless hours and gave up more than one holiday to create a report that aims to finally answer these concerns about liability. In the process, we had hours of robust conversation and had friendly but probing disagreements. We taught each other concepts of regulatory science, medicine, business, law, and ethics. And in the end, we found agreement and solutions, all in a mission to support the millions of pregnant and lactating women who, in a very real sense, represent the future of this country.

Many of the people on this committee and those who have supported its work have been waiting for decades to see pregnant and lactating

women appropriately supported through clinical research. The United States' current record on maternal and newborn health is weak and unworthy of a country that is capable of scientific and medical wonders. It is my hope that as you read the report, you will sense the urgency of its key messages and find a way to act on them, whatever your role may be in the clinical research enterprise. Our recommendations are comprehensive, but they are far from daunting. I hope that in the coming decade, if my children and their partners choose to join the millions of pregnant and lactating women each year in the United States, that they will do so with confidence that the medical treatments they may need are as safe and effective as possible.

Margaret Foster Riley, *Chair*
Committee on Developing a Framework to Address Legal, Ethical, Regulatory, and Policy Issues for Research Specific to Pregnant and Lactating Persons

Summary

Pregnant and lactating patients and their clinicians must currently make decisions regarding what drugs and vaccines they should use during pregnancy and lactation without the benefit of high-quality evidence regarding the products' safety and efficacy. The inadequacy of that evidence prompts some pregnant and lactating women to forgo necessary treatment, which results in harm to them or their fetus or child, while others decide to use the medical product, which entails an unknown likelihood of harm and provides uncertain benefits.

Before medical products are licensed, they must undergo clinical studies to evaluate the efficacy, safety, and appropriate dosage in the populations in which they would be prescribed. Policies on clinical research require that the participants in clinical studies be as diverse as the expected patient population. Nonetheless, pregnant and lactating women continue to be excluded from most clinical studies to the detriment of their health and that of their fetuses and children. Past studies have attributed their exclusion to concerns about legal liability for the investigators and institutions that conduct and sponsor clinical research should research participants, or their fetuses or children, experience negative effects from the study intervention. Yet the committee has found limited evidence of such liability. Rather, excluding pregnant and lactating women from clinical research appears to increase the potential for harm, and by extension liability, when medical products are marketed without relevant information from research with pregnant and lactating women. Generating and reporting data about the safety, efficacy, and dosage of

medications in pregnant and lactating women would reduce the latter sort of liability. To generate such data, policies need to counteract existing disincentives to the responsible and ethical inclusion of pregnant and lactating women in clinical studies.

The committee offers nine recommendations for action by Congress, Department of Health and Human Services, National Institutes of Health, Food and Drug Administration, Office for Human Research Protections, and clinical investigators, which if implemented would result in the appropriate inclusion of pregnant and lactating women in clinical research and thus provide more of the evidence that they and their health care providers need to make informed health care decisions.

A DANGEROUS LACK OF INFORMATION AND THE BENEFITS OF RESEARCH

Each year in the United States, more than 3.5 million individuals give birth, and some experience serious diseases or conditions that are unique to pregnancy, including gestational diabetes, preeclampsia, and severe nausea and vomiting. Being pregnant also makes them more likely to acquire, or experience worse outcomes from, infectious diseases such as influenza and COVID-19. Pregnant women—and the nearly 3 million women who initiate breastfeeding each year—also experience the same diseases and conditions as other adults, such as depression, diabetes, hypertension, cancer, lupus, and human immunodeficiency virus (HIV). If left untreated, those conditions threaten the health and lives of pregnant and lactating women and their fetuses and children.

Seventy percent of pregnant women take one or more prescription medications during pregnancy, as is also true for at least half of lactating women. Pregnant and lactating women are generally excluded from clinical studies; they and their health care providers lack the sort of data about the dosage, efficacy, and safety of medical products that are available for other members of the adult population. Although pregnancy and lactation are physiologically unique, pregnant and lactating women and their clinicians must usually rely on data derived from clinical studies in nonpregnant and nonlactating adults, as well as from any preclinical studies in pregnant and lactating animals.

While pregnant and lactating women are permitted to use licensed products, the absence of relevant evidence not only presents individuals with a conundrum about how to proceed but also, at the population level, erects barriers to delivering safe, effective, and timely therapeutic and preventive measures, thus exacerbating existing health inequities for pregnant and lactating women.

The absence of a sufficient evidence base means that almost all pregnant and lactating women with a condition for which a medical product might be appropriate are, in effect, participants in large, uncontrolled experiments that typically will not produce useful data. Not surprisingly, a consensus has arisen in recent years that the more ethical and responsible course would be to include pregnant and lactating women in clinical research. In sum, the benefits to pregnant and lactating women of being included in well-designed, ethical clinical research on medical products is now generally accepted. Yet such studies are still not routinely conducted.

THE COMMITTEE'S TASK

In 2016, Congress authorized the creation of the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC Task Force) to evaluate gaps in knowledge about safe and effective therapies for pregnant and lactating women. In its 2018 report, the PRGLAC Task Force noted that the possibility of legal liability is frequently cited as a reason for not enrolling pregnant and lactating women in clinical research or for dismissing trial participants who become pregnant. Legal liability refers to a party's breach of duty that results in harm to another. To address this concern for liability, Congress called on the National Academies of Sciences, Engineering, and Medicine to convene a committee to examine the real or perceived risk of liability arising from research conducted with pregnant and lactating women.

The statement of task asked the committee to study the evidence and report "findings, conclusions, and recommendations for safely and ethically including pregnant and lactating persons in clinical research that substantially mitigates or avoids incurring liability." The statement of task also asked the committee to develop a matrix of relative liability to various stakeholders for medical product development. After reviewing the evidence, the committee concluded that a matrix would be subjective rather than based on empirical analysis because the bounds of liability are imprecise and quantifying relative liability is not possible. Therefore, a matrix would give a mistaken illusion of scientific precision. The committee instead thoroughly examined liability for harms alleged to have occurred during clinical research and in the clinical use of licensed medical products. The committee complemented this examination with a discussion of the laws and regulations applicable to clinical research involving pregnant and lactating women in order to explore when and how liability arises. This approach illuminated the relationship between legal liability—and perceptions thereof—and other regulatory, economic, and social influences on pregnant and lactating women's exclusion from clinical studies.

THE LIABILITY LANDSCAPE

The collection of safety and efficacy data in clinical research raises potential liability concerns stemming from evidence of potential harm that may arise from use of an investigational product. The possibility of injury to a child who was exposed to an investigational product in utero or while breastfeeding is of primary concern to research participants. These concerns also affect other stakeholders involved in clinical research. An injury could tarnish the sponsoring company's reputation and diminish public trust in its other products. The potential for injury to a child also creates fear of a court trial in which their every decision and action is scrutinized publicly, leading possibly to a large damage award. Scrutiny may be magnified for an injured child who did not choose to take the risk and may live with the injury for a lifetime.

If an approved medical product injures the fetus or child of pregnant or lactating women, the total amount of harm done could be much greater than what would occur in a clinical trial. Thus, failing to have conducted rigorous and regulated trials with pregnant and lactating women potentially shifts the risks of harm from the small number of well-monitored pregnant and lactating women and their offspring in the trials to the larger number in clinical settings. This failure also seems to increase the potential liability of the individuals and organizations who manufacture, distribute, and prescribe the medical product without providing dosing, safety, and efficacy information that is relevant to a distinct group of patients who are expected to use the product. That said, manufacturers have generally mitigated this risk through labeling, promotion, and postmarket surveillance in accordance with FDA regulations and guidance, rather than by including pregnant and lactating women in clinical research. If injury does occur, manufacturers may argue that they had neither knowledge of possible risks relating to use of the product in pregnant and lactating women nor a duty to acquire such knowledge in the absence of any FDA requirement to test in these populations.

A case law analysis revealed no reported claims of liability for research-related injuries relating to lactating women's participation in clinical research. One marketed drug was the subject of several reported cases involving injury to the lactating woman, without injury to the child. The committee found no reported cases relating to participation of pregnant women in clinical trials since 1962 when the U.S. Food and Drug Administration (FDA) was granted the authority to require proof of safety and efficacy of products before they go on the market. There were, however, many cases involving liability claims related to pregnant women's use of on-market drugs approved for treatment of conditions in the adult population.

Although there are limitations to the review of the case law—including that the likelihood that encountering liability is diminished by the reality that many clinical trials exclude pregnant and lactating participants, and that the analysis partially relies on extrapolation from general knowledge about the regulatory context and litigation regarding pharmaceutical products—the analysis revealed three important points.

1. Little evidence exists of liability resulting from including either lactating or pregnant women in clinical trials.
2. Little evidence has been found that lactating women's use of approved and marketed products gives rise to liability.
3. There is substantial evidence of liability related to pregnant women's use of approved and marketed products, and some evidence that aspects of that liability might have been avoided had pregnant women been included in the clinical trials for those products.

In light of these findings, the committee considered drivers of the perception that including pregnant and lactating women in clinical studies creates a high liability risk. Perceptions of liability appear to be based in fear of uncertainty, given that those involved in clinical research with pregnant and lactating women have a poor understanding of the risks of harm, legal liability, and how other factors may contribute to liability. The perception of liability is also shaped by the cultural significance of preventing fetal harm linked to actions taken by pregnant women. Consequently, the public, policy makers, and others perceive research involving pregnant and lactating women as legally risky. *The reality is that not conducting research involving pregnant and lactating women has the potential to generate far greater harm arising from treatments and preventives that have not been tested in pregnant and lactating women, and thus a greater risk of liability for all those associated with the clinical encounter to the extent that they are found to have violated a duty under applicable state tort law.*

ABATING LIABILITY BY REDUCING POTENTIAL HARM

Harm and liability are interconnected: harm refers to the injury suffered; liability refers to the legal responsibility for that harm. Notably, harm can result from inclusion in clinical research as well as exclusion from clinical research. Employing strategies to reduce potential harm can play a role in mitigating both liability and the effect of *perceived* liability arising from a pregnant woman's research participation. The current drug development pathway and the protections offered through clinical

research regulations have been instrumental in reducing harm to research participants and patients. However, there are opportunities to improve current regulatory systems to further minimize harm for research involving pregnant and lactating women.

Clinical research is essential for advancing scientific knowledge and improving health outcomes. However, the exclusion of pregnant and lactating women from clinical studies can produce harm resulting from inadequate or inappropriate treatment or nontreatment in the absence of adequate evidence. Producing data by conducting research with pregnant and lactating women reduces this harm. Doing so responsibly requires strategies to mitigate the potential harm from including them in research.

Clinical studies conducted with pregnant and lactating women raise distinct considerations related to risk–benefit assessments because of the physiological differences in pregnancy and lactation and, significantly, the intimate relationship of the research participant and the fetus or nursing child who may be directly or indirectly exposed to unknown or uncertain risk from the investigational product.

Clearer guidance from the U.S. Food and Drug Administration (FDA), detailing the expected study designs, safeguards, and product-specific monitoring for conducting clinical studies with pregnant and lactating women would equip sponsors and investigators with crucial information for safely executing these trials, and compliance with such guidance, though not a formal defense, manifests due care and hence may reduce the likelihood of being found liable. Moreover, the Office for Human Research Protections (OHRP) under HHS offers guidance to institutional review boards (IRBs) on interpreting HHS regulations. However, ambiguity in HHS regulations for including pregnant women in clinical research, particularly related to the concept of minimal risk, leads IRBs to reject studies that propose including pregnant women. Research sponsors can also design clinical research using innovative methodologies and can increase equity through pragmatic trials and opportunistic studies.

MITIGATING POTENTIAL LIABILITY IN CLINICAL INVESTIGATIONS

The legal liability that is relevant to the participation of pregnant and lactating women in clinical research is tort liability. This branch of law aims to compensate parties who have been injured by the negligent or wrongful acts or omissions of others or by products or conditions that create undue risk. Tort liability also encourages reasonable and responsible behavior to reduce future harm. In the context of clinical care and research, part of health care professionals' responsible behavior is providing patients and research subjects with a clear, complete, and

comprehensible description of the potential benefits and risks of a medical intervention and of alternatives as part of the process of obtaining their informed, voluntary consent. Along with clear regulatory guidance on protecting participants from harm, strengthened informed consent processes could help mitigate potential liability.

In some situations—especially when actors have departed from the applicable standard of care—reaching an individualized judgment about liability is important for fulfilling tort law's remedial and deterrence objectives. However, the process is time consuming, expensive, and arduous for all concerned. No-fault compensation provides an attractive alternative because it eliminates the burden on the harmed individual to prove their injury is the result of another's breach of duty, and it mitigates liability for those who may be the subject of a lawsuit through the tort system. Permitting U.S. investigators to use federal grant funds to purchase clinical trial insurance, which offers no-fault compensation plans, could help mitigate the liability concerns of institutions and investigators.

Following the 2022 Supreme Court decision in *Dobbs v. Jackson Women's Health Organization*, the breadth of privacy issues for pregnant research participants may increase as states propose and enact new laws aimed at preventing abortion, protecting fetal life, and regulating the choices of pregnant women. Overall, the *Dobbs* decision is likely to increase liability for including pregnant women in clinical research. It is yet unclear how the *Dobbs* decision and newly passed or enforced state laws will affect pregnant women's willingness to participate in research and sponsors' and research institutions' willingness to support research in states that may penalize fetal harm. Certificates of confidentiality (CoCs) can be a valuable tool to protect research participants against privacy issues and could address pregnant participants' concerns that their health information will be shared. CoCs likely provide privacy protections in many of the contexts involving pregnant and lactating women in clinical research.

FACTORS INFLUENCING PERCEPTIONS OF LIABILITY

The committee determined that decisions regarding research with pregnant and lactating women are influenced by perceptions of liability that are intertwined with other factors that have contributed to the exclusion of pregnant and lactating women from clinical studies. When a sponsor or other stakeholder is deciding whether to conduct research with pregnant and lactating women, it evaluates the reasons for and against doing the research—incorporating considerations related to uncertainties and assessments of legal liability exposure, potential reputational losses, and financial, technical, and practical considerations associated with the

complexity of the trial, among others. This includes the regulatory reality that FDA does not require that research be conducted with pregnant and lactating women in order to market a product to the adult population. If the considerations against doing the research outweigh those in favor of doing the research, the sponsor and others are likely to decide not to conduct the research. Each stakeholder's decision weighs the potential for liability along with other factors, including

- the culture of exclusion;
- challenges in recruiting participants;
- lack of expertise in research involving pregnant and lactating women;
- reputational risk;
- cost and complexity of trials; and
- lack of financial incentives.

Changing one factor, such as offering regulatory predictability or financial incentives, could offset and overcome potential liability concerns; addressing these interrelated factors together could affect how stakeholders view liability regarding research with pregnant and lactating women.

Recommendations

The committee drew on public testimony, research, and deliberations to arrive at nine recommendations to improve the safe and ethical inclusion of pregnant and lactating women in clinical research while mitigating the risk of liability. The recommendations address liability with attention to the multiple stakeholders involved along the medical product development pathway and the ways in which they perceive liability. The recommendations address the liability risk—and perceptions of liability risk—of various stakeholders through three interconnecting approaches. The first is through strategies that directly mitigate liability. The second is through strategies that minimize harm, and therefore diminish the potential for liability. The third approach involves addressing the factors that discourage the inclusion of pregnant and lactating women in clinical research that sponsors and researchers weigh alongside the potential for liability.

Recommendation 1. 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.

a. **The revised guidance should set forth the study designs, safeguards, and product-specific monitoring expected for conducting clinical studies with pregnant and lactating women, and include considerations for how sponsors should determine appropriate study designs, safeguards, and product-specific monitoring.**
b. **The revised guidance should make clear that research plans and all necessary study protocols are prepared, research sites are identified, and monitoring and oversight committees are appointed for pharmacokinetic, pharmacodynamic, and dosage determination studies with pregnant and lactating women while Phase III studies for the product are being carried out in the general adult population.**
c. **The revised guidance should specify contents of a streamlined Investigational New Drug Application for use by academic and other noncommercial sponsors to study a drug in pregnant and lactating women in the event that studies are not initiated and completed in a timely manner by the New Drug Application, Biologics License Application, or Premarket Approval holder as contemplated by the guidance.**
d. **The revised guidance should make clear the requirement to conduct studies with pregnant and lactating women is dependent upon (i) the product having the potential for use by pregnant and lactating women and (ii) that use being consistent with available clinical and preclinical safety and efficacy data in these populations. If the product sponsor believes that data from preclinical studies of the product, or evidence concerning the safety of other products in the same class, raises concerns about the potential harm to pregnant and lactating women or their offspring, the sponsor may submit to FDA a justification for not including pregnant or lactating women in the clinical studies outlining the basis**

for such for concerns and why the potential harms cannot be adequately prevented or mitigated in light of the potential benefits to these populations. If FDA reviewers agree with the justification, trials in pregnant or lactating women are not to be carried out and the safety information must be included in the drug labeling.

Recommendation 2. The U.S. Food and Drug Administration (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. FDA should revise its guidance relating to such diversity action plans to include the following:

a. **Formal discussion, such as during meetings before an Investigational New Drug Application is granted, on FDA's expectation for the inclusion of pregnant and lactating women in clinical trials of the product and on the sponsor's plans to include these populations in clinical trials.**
b. **Submission of, or if already completed, reference to relevant preclinical data that support the determination of dosage, safety, and efficacy in pregnancy and lactation, including developmental and reproductive toxicology studies and, as available, any safety data on pregnancy and lactation for other drugs in the same class. If the preclinical data presented in the diversity action plans raises safety concerns for conducting human trials in pregnant and lactating women, a justification for not conducting clinical studies must be submitted along with the diversity action plan outlining the evidence for concerns. When FDA reviewers agree there are safety concerns regarding clinical testing in pregnant and lactating women, trials are not to be completed and the safety information must be included in the drug labeling.**
c. **Plans for conducting pharmacokinetic and pharmacodynamic studies in pregnant and lactating women, including dosing studies through each stage of pregnancy. The plans for these studies should be submitted to the agency no later than the submission of a New Drug Application or Biologics License Application for the general population.**

Recommendation 3. 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.

- **a. OHRP should issue guidance that provides definitions and interpretation for 45 CFR 46, Subpart B, particularly "minimal risk" and "additional safeguards" that are conducive to the responsible and ethical inclusion of pregnant and lactating women in clinical research.**
- **b. OHRP should issue guidance to clarify the applicability of 45 CFR 46, Subpart D, for clinical research that enrolls lactating women who breastfeed their children during the study.**
- **c. OHRP should issue a list of frequently asked questions that could assist clinical researchers and IRBs to assess risk in clinical research that involves pregnant and lactating women and to provide justifications for the inclusion or exclusion of pregnant or lactating women in clinical research.**
- **d. OHRP guidance should, like FDA guidance, recommend that IRBs have experts in pregnancy, lactation, and neonates participate in the review of study protocols involving such participants.**
- **e. The OHRP Division of Education and Development should offer training and outreach for researchers and IRBs to develop expertise in research in pregnancy and lactation.**
- **f. OHRP should create a subcommittee for research with pregnant and lactating women within the Secretary's Advisory Committee on Human Research Protections that will provide detailed recommendations on how to conduct more research with pregnant and lactating women safely and ethically.**

Recommendation 4. 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. This legislation should:

- **a. Direct the director of the National Institutes of Health, in consultation with the commissioner of the Food and Drug Administration (FDA) and experts in pregnancy and lactation, to develop and publish annual prioritization lists of both on-patent and off-patent approved medical products for which additional studies are needed to assess the dosage, safety, and effectiveness of the use of the medical products in pregnant and lactating women.**
- **b. Direct the secretary of the Department of Health and Human Services (HHS) to award contracts to entities that have the expertise to conduct clinical studies in pregnant and lactating women to study medical products that are no longer subject to relevant patent or exclusivity protections, thus enabling the entities to conduct studies in pregnant and lactating women of one or more of the off-patent medical products identified in part (a) of this recommendation.**
- **c. Grant the secretary of HHS the authority to make a written request to the patent holder of medical products subject to patent or exclusivity protections to conduct clinical studies involving pregnant and lactating women concerning one or more of the on-patent medical products identified in part (a) of this recommendation.**

    - **i. To incentivize manufacturers to complete these studies, Congress should create incentive programs, such as extended market or data exclusivity or tax breaks, to the holder of the approved application if studies are completed within the requested time frame and data are submitted to FDA for inclusion in product labeling.**
    - **ii. This incentive program should be authorized for an initial 5-year period, with reauthorization based on experience with the program and a determination of whether continuation is necessary.**

Recommendation 5. 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.

a. Congress should direct the secretary of the Department of Health and Human Services to require any entity that submits an application for a new drug, biologic, vaccine, or medical device, or a supplement for a new indication, new dosage form, new dosing regimen, or new route of administration, to submit data on the dosage, administration, safety, and effectiveness of its use in pregnant and lactating women.
b. Congress should amend Section 505(o)(3)(B) of the Federal Food, Drug, and Cosmetic Act to include "(iv) to identify and characterize risks to pregnant and lactating women and their offspring" as a justification for requiring postmarketing studies and postmarketing clinical trials.
c. To ease the initial challenges that may be faced in implementing this requirement, Congress should create programs, such as extended market exclusivity or tax breaks, for the holder of an approved New Drug Application, Biologics License Application, or Premarket Approval when studies are completed within the required time frame and data are submitted to FDA for inclusion in product labels. These programs should expire after several years, once sponsors have experience conducting these studies.

Recommendation 6. 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 7. 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 8. 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. From within its membership, the task force should identify agency leads to carry out the following activities:

- **a. Develop a central repository to collect postmarketing safety data from pregnancy and lactation exposure registries and database studies.**
- **b. Release guidelines on the content and format of data to be submitted to the central repository from existing pregnancy and lactation exposure registries, which should include, at a minimum, the following: number of pregnant and lactating women enrolled to date, number of pregnant and lactating women with unknown outcomes, number of pregnant and lactating women with pending outcomes, number of pregnant and lactating women lost to follow-up, and number and types of adverse events reported in pregnant and lactating women.**
- **c. Adopt standards requiring that the electronic health records of pregnant and lactating women be capable of being linked with records for their offspring in research databases.**
- **d. Evaluate the infrastructure, data elements, and resources that would be required to develop and maintain a centralized national registry for collecting and evaluating postmarketing data from pregnant and lactating women.**

Recommendation 9. 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.

1

Introduction

Ideally, all people who become pregnant and desire to remain pregnant would have healthy pregnancies, birth healthy babies, and have the ability to provide human milk to their children. However, some pregnant people get sick, and some sick people become pregnant. To ensure the health and well-being of pregnant and lactating women and their fetuses and newborns, evidence is needed on the safety, effectiveness, and proper dosage of medical products that these individuals may need to take during the perinatal period. Sufficient data on safety and effectiveness allow health care providers and patients to make informed decisions about an intervention's potential benefits and risks. In the face of insufficient evidence, a health care provider and a patient are in a difficult position: A decision to forgo an intervention may result in harm from an untreated or unprevented condition, while a decision to use an intervention puts the patient, the fetus, and the child at an uncertain risk of harm for an uncertain benefit.

That is precisely the situation that commonly confronts pregnant and lactating women when making decisions about therapeutic or preventive interventions. Although pregnancy and lactation are physiologically unique, pregnant and lactating patients and their clinicians must usually rely on data derived from clinical studies in nonpregnant and nonlactating adults, and preclinical studies in pregnant and lactating animals (Byrne et al., 2020). On an individual level, the evidence gap leads to avoidable harm to pregnant and lactating women and their offspring when a medication's dosage makes it ineffective, when its harm

outweighs its expected benefits, or when the lack of safety data leads a patient to reject a medication that would have been helpful. On a population level, the evidence gap affects pregnant and lactating women's access to safe, effective, and timely therapeutic and preventive measures, reduces the ability to develop responsive policies to identify and address health priorities in pregnant and lactating women and their children, and exacerbates existing health inequities.

Society benefits from the knowledge generated through clinical research. Data gathered through clinical research enable the development of safer and more effective therapies and vaccines, promote safer and more effective use of those medical products, and improve human health and health equity. Conducting clinical research with pregnant and lactating women allows these populations to experience the same benefits afforded to other populations who have data available on the dosage, safety, and efficacy of medical products. Because of the direct link between the health and well-being of pregnant and lactating women and that of their fetuses and children (Harris, 2000), children also stand to benefit from clinical research conducted with pregnant and lactating women. To improve maternal health, as well as newborn health and survival, it is imperative that pregnant and lactating women be included in clinical research.

This chapter begins with a discussion of the social benefits of research involving pregnant and lactating women and is followed by an exploration of the human cost of inadequate data, explores the sources of the inadequate data, provides a background to the study, and ends with the committee's approach to their charge.

THE HUMAN COSTS OF INADEQUATE DATA

Pregnant and lactating women with acute or chronic conditions must make difficult decisions about their health every day. These difficult decisions are compounded by a widespread lack of evidence on the dosage, safety, and efficacy of medical products in these populations, leaving health care providers and the more than 3.5 million patients who give birth each year and the more than 3 million patients who breastfeed in the United States without the critical evidence needed to make informed treatment decisions (Osterman, 2023). These issues are further complicated for racially minoritized pregnant and lactating women, specifically Black and American Indian and Alaska Native populations, who, owing to systemic and structural factors such as racism, bias, and inequitable access to health care, experience higher rates of maternal mortality and morbidity (Hill et al., 2022) and lower rates of breastfeeding initiation, duration, and exclusivity (Jones et al., 2015).

Inadequate data harm pregnant and lactating women, who have different physiological states, as well as the fetuses and breastfeeding children who are not only affected by drug exposure, but also the health of the pregnant or lactating woman. Although the committee briefly mentions women of reproductive age who could potentially become pregnant to appreciate the scope of the problem, pregnant women and lactating women are the focus of this report.

The Preconception Period

The preconception period includes women of reproductive age who may either have an unplanned pregnancy or who are preparing to become pregnant sometime in the future. Data reported from 2018 identify close to 73 million U.S. women of reproductive age (Guttmacher Institute, 2021).[1] Although many of these individuals are not intending to become pregnant, some are either seeking to become pregnant or may have an unplanned pregnancy. Many are taking medications before they become or know they are pregnant, often for chronic conditions. More than half of American adults have at least one chronic condition (Boersma et al., 2020), and most, if not all, individuals affected by chronic conditions require some type of medication or treatment, with adherence to the treatment being essential for optimal health (Unni, 2023).

While it would be inappropriate to treat all women of reproductive age as being potentially pregnant, clinicians treating potentially pregnant women face challenges prescribing medications to these individuals without data on their safe use during early pregnancy. Early pregnancy is a time of physiological changes in the pregnant woman and the start of fetal development. Without human data on medication use during this critical period, clinicians must make treatment decisions for their patients without knowing how medication use during this period may affect any potential future pregnancies. However, only 11 percent of drugs approved between 2010 and 2019 included human data to guide prescribing for pregnant women (Byrne et al., 2020), which makes preconception prescribing difficult.

Further challenges arise for unintended pregnancies, which make up over 40 percent of all pregnancies in the United States (CDC, 2023c). Teenagers and women in their early 20s are groups with higher proportions of unintended pregnancy. Unintended pregnancies are associated with a higher risk of exposure to teratogenic substances—a substance capable of causing congenital malformations (Han et al., 2005). A recent study

[1] Article defines reproductive age as 15–44 years.

found that 1 in 16 women took a known or potentially teratogenic agent during pregnancy, with elevated risk of prenatal exposure in teenagers and women 45 and over (Sarayani et al., 2022). Without human data on the effects of medical products in early pregnancy, clinicians are unable to provide the best health care and cannot address potential harm in treating women who are intending to or may become pregnant.

Pregnancy

More than 3.5 million women give birth annually in the United States (CDC, 2023a), and as of 2019, there were an estimated 5.5 million pregnancies each year (HHS et al., 2023). Ninety percent of pregnant women reportedly take some type of medication during pregnancy, with 70 percent taking a prescription medication (Mitchell et al., 2011). It is not uncommon for pregnant women to take multiple medications—13 percent report taking five or more prescription medications (Haas et al., 2018). The medications taken by pregnant women may be for a preexisting condition or for a condition related to pregnancy (see Box 1-1).

Pregnancy leads to a number of physiological changes across all three trimesters that can affect how the body handles and responds to medications, including changes in the cardiovascular, respiratory, gastrointestinal, metabolic, and renal systems (Kepley et al., 2023). Box 1-2 describes these physiological changes throughout different trimesters in greater detail. Despite these physiological changes, very few medications approved by the U.S. Food and Drug Administration (FDA) have human pregnancy data available, though most (90–93 percent) have pregnancy safety data from animal models (Byrne et al., 2020; Mazer-Amirshahi et al., 2014). From 2010 to 2019, only 11 percent of approved medications had human pregnancy data available (Bryne et al., 2020). Moreover, there is insufficient development of treatments for conditions specific to pregnancy, such as gestational diabetes and preeclampsia (Caritis and Venkataramanan, 2021).

This lack of human data has serious consequences for pregnant women and their fetuses. Without data on proper dosage, safety, and efficacy on medication use in pregnant women, health care providers and their patients must make difficult decisions about whether to use a medication to manage health without safety information or discontinue a medication and potentially put the pregnant woman's health and the health of the fetus at risk. In a patient story submitted to the committee, one patient with rheumatoid arthritis (RA) described this difficult decision:

> For my second pregnancy, which began in 2013, I was also advised to stop all of the medications that I had been using to control my RA. Unfortunately, this time my RA flared badly during pregnancy. By the time

BOX 1-1
Common Conditions and Treatments in Pregnancy

The Centers for Disease Control and Prevention (CDC) identified the most common complications during pregnancy; they are anemia, anxiety, depression, diabetes (including gestational diabetes), heart conditions, high blood pressure (including preeclampsia), nausea and vomiting, and infections (CDC, n.d.). Each of these conditions may require therapeutic interventions. Pregnant women are at least as susceptible to conditions and diseases as the general population, but when compared to nonpregnant women, pregnant women are more likely to be severely affected by infections. Examples include the influenza virus, hepatitis E virus (HEV), herpes simplex virus (HSV), and malaria parasites (Kourtis et al., 2014). Additionally, pregnant women were hospitalized for COVID-19 infections at a higher rate than nonpregnant women (Ellington et al., 2020).

In addition to infectious diseases, pregnant women are also at higher risk of developing or worsening chronic conditions during pregnancy. A study of 8.1 million hospital deliveries in the United States found that over 600,000 pregnant women (7 percent) had at least one common chronic condition (Admon et al., 2017). For example, from 2013 to 2014 the rate of asthma was 40 cases per 1,000 hospital deliveries, 23.6 cases per 1,000 for chronic hypertension, and 10.3 cases per 1,000 for preexisting diabetes. The prevalence of multiple chronic conditions in pregnancy was 8.1 per 1,000 hospital deliveries (Admon et al., 2017).

According to Medicaid prescription data, the most commonly dispensed medications during pregnancy were for infections, including nitrofurantoin (21.6 percent), metronidazole (19.4 percent), amoxicillin (18 percent), azithromycin (16.9 percent), and promethazine (13.5 percent) (Palmsten et al., 2015). Of the previously listed drugs, only amoxicillin has controlled human data in pregnancy and lactation (FDA, 2006). Animal studies have been completed for the others, two of which have documented adverse effects on animal fetuses (promethazine, nitrofurantoin) (FDA, n.d., 2009). The FDA Office of Women's Health is currently funding research to describe the drugs that pregnant and lactating women commonly use, and changes in use trends over time (FDA, 2021).

> I hit my third trimester, I was struggling so significantly that my doctors advised me the uncontrolled inflammation in my body was more of a risk to my baby than restarting my RA medications would be. Based on pretty limited data, I ended up restarting the same biologic I had been advised to avoid during my first pregnancy. This was a very uncomfortable and difficult decision to make.

Because evidence in humans has not been generated on the safety, efficacy, and dosing for medical products during pregnancy, some individuals will decide to forgo use of a medical product that would benefit their health and support the development of a healthy fetus. Others may decide to continue use of a medical product and find that the dose that they used prior to becoming pregnant is no longer providing effective treatment (Little and Wickremsinhe, 2017).

Box 1-2
Physiological Changes and the Implications for Use of Medications

During pregnancy and lactation, there are dramatic changes in the body's physiological processes, and these changes have implications for how medical products are absorbed, metabolized, distributed, and eliminated by the body. These changes occur during and throughout the stages of pregnancy and during the postpartum period. Thus, it is critical that pregnant and lactating women be included in clinical research to better understand how medications may affect pregnant and lactating women and women who are not pregnant and lactating differently and to help guide clinical decision making.

Physiological Changes During Pregnancy

Physiological changes begin immediately upon fertilization and affect nearly all systems in the body, including the endocrine, cardiovascular, respiratory, hematologic, renal, and gastrointestinal systems (Kepley et al., 2023). These changes include the following:

Endocrine: Rising levels of hCG stimulate the production of progesterone and estrogen and prevent further ovulation, while other hormones also rise, including thyroid-stimulating hormone for brain development, and prolactin to stimulate milk production. Increased levels of relaxin allow connective tissues to soften, and the body produces mores endorphins to counteract labor pain.

Cardiovascular: Changes in the cardiovascular system include increased heart rate, stroke volume, cardiac output, and decreased vascular resistance. Increased cardiac output directs blood to the uterus, placenta, kidneys, skin, and extremities; the increase in blood flow contributes to a rise in skin temperature.

Respiratory: Increased pressure from the enlarging uterus decreases residual volume and expiratory reserve volume, but an increase in inspiratory reserve volume keeps vital capacity the same as prepregnancy levels. Respiration is stimulated by higher levels of progesterone and can lead to hyperventilation.

Hematologic: Blood volume increases by around 1.5 liters during pregnancy, and red blood cell mass increases by approximately 30 percent; these changes help deliver oxygen to the fetus but increase the need for iron. As pregnancy progresses, elevated levels of clotting factors increase the risk of deep vein thrombosis.

Renal: Increased blood flow to the kidneys during pregnancy results in increased glomerular filtration rate (GFR) and renal plasma flow. Increases in progesterone and relaxin lead to dilation of the urinary collecting system, increasing the risk of urinary tract infections and pyelonephritis with asymptomatic bacteriuria.

Gastrointestinal: Multiple factors present in pregnancy—including delayed gastric emptying, increased small bowel transit time, reduced muscle tone of the lower esophageal sphincter, and compression attributable to uterine growth—make gastroesophageal reflux disease common in pregnant women.

Implications for Medication Use

These changes and many others that occur during pregnancy have implications for the safety and efficacy of medications, owing to changes in the absorption, metabolism,

BOX 1-2 Continued

distribution, and elimination of drugs (Eke et al., 2023). The implications are too numerous to list here; the following includes selected examples:

Absorption: Drug absorption can be affected by pregnancy-related physiological changes, and these effects vary by route of administration. For example, increased blood flow may affect the absorption of injected drugs (Eke et al., 2023). Delayed gastric emptying may affect orally administered medications, while the absorption of inhaled medications is enhanced owing to increased blood flow (Eke et al., 2023).

Metabolism: The actions of drug metabolizing enzymes, including cytochrome P450, UGT1A4, and CBR1, have been shown to change during pregnancy, with some increasing in activity and others decreasing (Tasnif et al., 2016). CYP450 enzymes are responsible for metabolizing around 75 percent of all drugs in current clinical use (Zanger and Schwab, 2013), so understanding the action of these enzymes is critical for the safe and effective use of medication in pregnant and lactating women.

Distribution: Increases in body weight, fat stores, and blood volume affect how drugs are distributed throughout the body. For example, there are substantial differences between pregnant and nonpregnant women in the distribution of buprenorphine, a lipophilic partial opioid agonist used to treat individuals with substance use disorders (Eke et al., 2023).

Elimination: Many systems are involved in drug excretion, but kidneys are the primary organ for elimination. During pregnancy, the increase in renal blood flow, plasma flow, and GFR increases the excretion of most drugs (Eke et al. 2023). The increase in renal clearance can lead to subtherapeutic levels of renally eliminated drugs (Kepley, 2023).

Lactation and Medication

The safety and effectiveness of medications are affected by the physiology of lactating women and their children, as well as the properties of human milk. Lactating women undergo physiological changes such as increased blood flow to the breasts, increased bone loss, and changes to the intestinal, renal, metabolic, and hormonal systems (Canul-Medina and Fernandez-Mejia, 2019); these changes may affect drug metabolism and distribution. However, the major concern during lactation is the transfer of medication into the breast milk and subsequently into the infant. Whether and how much medication transfers to the infant depends on maternal serum concentration and the pharmacologic properties of the medication (Spencer et al., 2022). The effect of drug exposure on the infant is largely dependent on age and size; neonates in particular have physiological differences that affect drug absorption, metabolism, and elimination (Alcorn and McNamara, 2002). However, approximately 90 percent of marketed drugs are considered safe for breastfeeding given the dose received by infants in human milk (Newton and Hale, 2015).

Lactation

According to the Centers for Disease Control and Prevention's (CDC) *Breastfeeding Report Card, 2022*, of those infants born in 2019, 83 percent started out receiving human milk, with almost 79 percent receiving any human milk at 1 month and 56 percent at 6 months (CDC, 2022b). A small U.S. study from 2007 found that nearly all the breastfeeding women enrolled in the study used at least one medication (Stultz et al., 2007). Larger studies conducted abroad suggest that at least 50 percent of breastfeeding women take at least one medication (Saha et al., 2015). Many of these women are concerned about taking medications while breastfeeding and the effects it can have on their child (Etzel and Ambizas, 2022). For the vast majority of drugs, the amount of medication that enters human milk does not reach a level that is dangerous for the breastfeeding child (Halesmeds, 2022; Medsafe, 2015). However, the challenge is to determine which ones may be hazardous. Drugs are primarily transferred into human milk through passive diffusion, but other factors can also affect the maternal plasma-to-breast drug transfer, including maternal concentration of a drug and human milk fat content, as well as a drug's half-life, acidity, molecular weight, lipid solubility, degree of protein binding, and other physiochemical properties (see Box 1-2 for details). The exposure to medications in human milk vary over the course of the phase of lactation and infant feeding, with exposure decreasing as babies wean off human milk.

Those who are lactating may be taking medications for preexisting or lactation-specific conditions. However, similar to pregnancy, very few medications have human lactation data. From 2010 to 2019, 48 percent of approved medications had labels with no data on lactation, 49 percent had animal data, and less than 5 percent had human data (Byrne et al., 2020). Without human safety data in lactation, many lactating women may choose to cease lactation to take a medical product for their health or continue lactation and delay treatment of their health condition.

These decisions have consequences for both the health of the lactating mother and their breastfeeding child. A predictive model estimates that breastfeeding for less than the recommended first 6 months of a child's life produces excess maternal and infant mortality and increased health care costs (Bartick et al., 2017). Human milk provides the baby protection against critical infections and inflammation while contributing to improved infant immune response, gut microbiota, and organ development. For the lactating mother, breastfeeding can reduce the mother's risk of breast and ovarian cancer, type 2 diabetes, and high blood pressure (CDC, 2023b). Further, some conditions left untreated because of fear of medication use while breastfeeding can negatively affect the child as well as the mother. For example, untreated postpartum depression can affect the development of the child and can cause delays in language development, learning problems, increased crying or agitation, and behavioral problems (Stein et al.,

2014). Without evidence from clinical studies in humans on the safety of medication use during lactation, health care providers and their patients are not able to make informed decisions on their health.

CIRCUMSTANCES THAT HAVE LED TO INADEQUATE DATA TO GUIDE MEDICAL DECISION MAKING

There is growing recognition that multiple populations, such as older adults, people living with multiple chronic conditions, and pregnant and lactating women, are unjustifiably excluded from clinical studies (Shore et al., 2024). Inadequate data to inform the treatment of pregnant and lactating women is not a problem unique to the United States, as countries around the world are similarly struggling with limited data for these populations (Manningham-Buller and Brocklehurst, 2022; Thurin et al., 2022). There is a growing international consensus that the responsible and ethical conduct of clinical research with pregnant and lactating women is essential to generate reliable scientific data on dosage, safety, and efficacy. Public calls for inclusion have come from groups ranging from the World Health Organization, the Pan American Health Organization, and the Council for International Organizations of Medical Sciences, to the American College of Obstetrics and Gynecology (CIOMS and WHO, 2016; NICHD, 2018; PAHO and WHO, 2016; WHO, 2023b).

In the United States, researchers and advocacy groups—including the Zika and Beyond: Pregnancy, Research, and Public Health Ethics (PREVENT) and Pregnancy + HIV/AIDS Seeking Equitable Study (PHASES) projects of the Second Wave Initiative, (UNC, 2017), and the Coalition to Advance Maternal Therapeutics (CAMT)—have called for the inclusion of pregnant women in clinical research. In fact, both PREVENT and PHASES offer guidance on how to achieve ethical inclusion of pregnant women in clinical research. The exclusion of pregnant and lactating women from clinical studies has resulted in a dearth of evidence on the safety, efficacy, and dosing of medical products that are used or could be used by these populations. Without sufficient evidence generated through clinical research, pregnant and lactating patients and their clinicians must make decisions about treatment with medical products while not being able to fully assess the benefits and risks of treatment for their own health or that of their fetus or child.

For much of the latter half of the twentieth century, clinical research failed to adequately include women generally, and women of childbearing potential specifically (Merkatz, 1998). Following the revelations of the in utero harms from thalidomide use (see Chapter 2), research involving women of childbearing potential was deemed to be too risky for fear of harming developing fetuses if the research participant become pregnant during the study. In 1977, FDA issued guidance recommending against

including women of childbearing potential in early phases of clinical research (FDA, 1977). However, in the years that followed, scientific and public concern grew that using data from clinical research conducted in White males lacked scientific validity for the diverse populations that would go on to use the medical products after approval (IOM, 1994b).

In response, Congress passed the National Institutes of Health (NIH) Revitalization Act in 1993, which required that women and racial and ethnic minority populations be included in clinical research supported by NIH.[2] Progress has been slow and unequal. Though the representation of White women in clinical research has improved, other groups, such as racial and ethnic minority groups, older adults, and pregnant and lactating women are still underrepresented in clinical research (NASEM, 2022).

In 2016, Congress addressed the lack of human data on medical products used during pregnancy and lactation when it established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC Task Force) in the 21st Century Cures Act (Public Law 114-255). This task force was asked to identify gaps in research and knowledge, examine ethical issues, and make recommendations for the safe and effective use of medical therapies in pregnant and lactating women. The PRGLAC Task Force recommended that "this trajectory of exclusion be altered to include and integrate pregnant women and lactating women in the clinical research agenda" and presented 15 recommendations for conducting this research. Further, several international health groups, outlined in Box 1-3, have ongoing efforts to establish broader inclusion of pregnant and lactating women in clinical research.

One reason there is a lack of research involving pregnant populations is concern about fetal safety that reinforces decisions not to include pregnant women in clinical research. For example, the lack of human data on the safety of medical products in pregnancy creates anxiety about the unknown risks to the fetus, which causes sponsors and researchers to be hesitant about conducting research involving pregnant women, and ultimately leads to the continued dearth of dosing, safety, and efficacy data of medical products in pregnant women (Santye, 2016). However, the ethical concerns and potential risk of harms for lactating women are far less than for pregnant women, since the overwhelming majority of on-market products pose little risk to breastfeeding children, given their low concentrations in the breast milk (see Chapter 3 for further discussion).

A number of groups have now examined the ethics of conducting research involving pregnant and lactating women, and they have concluded that there is an ethical requirement to responsibly include pregnant and lactating women in research (Baylis and Ballantyne, 2016; IOM, 1994a; Krubiner et al., 2021; Lyerly et al., 2021; NASEM, 2023; NICHD,

[2] *Public Health Service Act*., Public Law 103-43, 103d Cong. (June 10, 1993).

BOX 1-3
Global Efforts for Broader Inclusion of Pregnant and Lactating Women in Research

There are growing efforts globally to address the health needs of pregnant and lactating women through research. Although this is not an exhaustive list, it is meant to show the growing international consensus that involving pregnant and lactating women in research is essential.

Council for International Organizations of Medical Sciences (CIOMS): In 2002, CIOMS released updated guidelines that stated that pregnant women should be eligible for participation in research (CIOMS, 2002). Their 2016 guidelines, prepared in collaboration with WHO, states that "Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted" (CIOMS and WHO, 2016).

World Health Organization (WHO): In 2022, the World Health Assembly adopted resolution 75.8, which notes that "clinical trials on new health interventions are likely to produce the clearest result when carried out in diverse settings, including all major population groups the intervention is intended to benefit, with a particular focus on underrepresented populations."

In a supplementary report on the resolution, WHO notes that this includes "in particular pregnant and lactating women." WHO is now moving forward with a series of meetings focused on implementation strategies for this resolution (WHO, 2023b).

International Council on Harmonization (ICH): Inclusion of pregnant and breastfeeding individuals in clinical trials (E21) was endorsed as a topic by the ICH assembly in 2022. The goal of this guideline working group is to "provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials." This working group will put out a technical document in late 2024. FDA is a member of ICH and is involved in the development of the guidelines (ICH, n.d.).

Global Forum on Bioethics in Research (GFBR): Research in pregnancy was chosen as a topic for the 2016 GFBR meeting, given the 2016 Zika outbreak. One of the consensus themes that emerged from this meeting was that pregnant women should not be excluded by default and "should be included in research unless there are valid reasons specifically to exclude them" (Hunt et al., 2017).

2018; van der Graaf et al., 2018). Expanding clinical research to include pregnant and lactating women and developing the necessary data for treating these populations have clear benefits for pregnant and lactating patients and their health care providers, and the benefits of conducting this research expand beyond the pregnant and lactating population.

THE SOCIAL VALUE OF CLINICAL RESEARCH

The potential for societal value—the provision of benefit to society through innovative technologies and medications that improve health—is the primary commitment of biomedical and scientific research (NASEM, 2019). Promoting societal value implies not only direct health benefits for

some but also potential improvements in health equity. Health equity is defined as all people having the opportunity to achieve the highest level of optimal health and well-being (CDC, 2022a; WHO, 2023a). Clinical research is a means through which society understands human health and works toward achieving health equity. The generalizable evidence gained through biomedical discovery, development, and clinical research leads to new medical products that detect disease, reduce human suffering, improve well-being, and save lives. Ultimately, to justify exposing people to potential harms through clinical research, research must have some societal value or benefit (Emanuel et al., 2000).

Including pregnant and lactating women in clinical research allows for these populations to experience the benefits of clinical research that are currently available to other populations who are included in clinical studies and for whom rigorous safety and efficacy data are available. Since 1962, all drugs entering the market must provide evidence of safety and efficacy for "conditions prescribed, recommended, or suggested in the proposed labeling."[3] Since 1998, FDA New Drug Application (NDA) regulations have required human safety and effectiveness data to report on demographic subgroups, including age, gender, and race, as well as other subgroups likely to use the medication.[4,5] In 2012, Congress expanded those requirements to include an action plan that prioritizes better completeness and quality of subgroup data, identification of barriers to subgroup enrollment in clinical trials, and making those data more available and transparent.[6] However, pregnant and lactating women were not specifically referenced in this legislation. Although considerable work is needed to ensure more data are available for all population subgroups, very little progress has been made on research involving pregnant and lactating women. As recent efforts have highlighted in other population subgroups, prioritizing research needs in pregnant and lactating women helps prevent harm to these women and their offspring.

Pregnant and lactating patients and their clinicians must currently make decisions regarding medications during pregnancy and lactation without the benefit of high-quality evidence on their dosage, safety, and efficacy. That lack of evidence in humans may prompt pregnant and lactating women to forgo medications that are necessary for their and their fetus' or child's health or to be treated with ineffective dosing or inappropriate medication. This problem is especially highlighted for pregnant women, since pregnant women who need access to medications do not

[3] *Amendment, the Federal Food, Drug, and Cosmetic Act,* Public Law 87-781 (Oct. 10, 1962).
[4] *Investigational New Drug Application,* 21 C.F.R. 312.33.
[5] *Applications for FDA Approval to Market a New Drug,* 21 C.F.R. 314.50 (Feb. 22, 1985).
[6] *FDA Safety and Innovation Act,* 126 Stat. 993, 1092-94 (July 9, 2012).

have an alternative other than to forgo necessary medications or potentially risk harming their fetus. Although it is important for both the lactating mother and their child to have the option to breastfeed, lactating women do have the option to cease breastfeeding and use formula or donor milk for their child, should a lactating woman need to take a medication without available safety data.

Insufficient data on the use of medical products in pregnancy and lactation has implications for health equity. Maternal mortality and severe maternal morbidity continue to be some of the most serious public health crises in the United States, particularly among Black women, American Indian and Alaska Native (AIAN) women, and low socioeconomic status communities (Chinn et al., 2020; Kozhimannil et al., 2020). In fact, the United States has the highest maternal mortality rate in high-income countries, and that rate is more than twice that of 10 other wealthy countries (Chakhtoura et al., 2019; White et al., 2022). Since sufficient evidence on medical products is also not available to pregnant women in other countries with lower maternal mortality rates, the high rate of U.S. maternal mortality cannot fully be explained by the lack of high-quality data to guide treatment decisions. However, common causes of maternal mortality in the United States, such as preeclampsia (Joseph et al., 2021), have no currently available treatment options. Rates of maternal mortality in the United States have sharply risen from 2018 to 2021 with stark racial and ethnic disparities, and substantially higher rates exist among non-Hispanic Black women (69.9/100,000), compared to 28.0/100,000 among Hispanic, and 26.6/100,000 births for non-Hispanic White women (CDC, 2021).

Maternal mortality is linked closely to maternal morbidities, and racial/ethnic disparities are apparent for conditions including preeclampsia and postpartum hemorrhage, as well as adverse birth outcomes (preterm birth and low birth weight). These adverse birth outcomes lead to a life cycle of inequity linked to higher rates of infant mortality. A report from CDC showed that infant deaths have risen for the first time in 20 years—up 3 percent from the previous year (CDC, 2016). Although the report does not provide a cause for this increase in death in the first year of life, maternal health and access to human milk are closely linked to newborn survival and health. Infant mortality rates are also approximately two times higher in children born to Black and AIAN individuals compared to children born to White individuals (Hill et al., 2022). Thus, generating sufficient data on safety, efficacy, and dosage, along with increased access to and appropriate prescribing of medications to treat maternal illness in pregnancy and lactation, is a key strategy to address and reduce health disparities in the United States.

Chronic conditions, such as hypertension and cardiovascular disease, diabetes, and mental health conditions, increase the risk of adverse maternal outcomes (Brown et al., 2020). Additionally, a woman with multiple chronic conditions has 3.8 times the rate of severe maternal morbidity and mortality compared to people without chronic conditions (Admon et al., 2018). Addressing these serious scientific gaps and promoting maternal and infant health will require research that centers pregnant and lactating women and also addresses the social and structural determinants of health (Crear-Perry et al., 2021). Beyond the personal and emotional cost of this issue, maternal mortality has serious social and economic consequences for the United States generally (White et al., 2022).

The burden of chronic disease is disproportionately experienced by racially minoritized groups in this nation as a result of structured inequities and discrimination (Geronimus et al., 2006). This means that pregnant women of color, who are more likely to enter pregnancy with comorbid conditions and end pregnancy having experienced adverse health events, are disproportionately disadvantaged by the exclusion of pregnant women from clinical studies and the resultant lack of sufficient data to inform optimal care of their conditions. Further, because racially minoritized populations have historically been excluded and are currently underrepresented in clinical research and the burden of disease is compounded at the "intersection" of pregnant and lactating women of color (NASEM, 2022), research studies that include pregnant and lactating women will need to be intentional about using an intersectional framework during the recruitment and retention of racially minoritized populations to truly maximize societal value and improve health equity.

To reduce harm to pregnant women and their fetuses and allow pregnant women to benefit from the knowledge generated in clinical research, it is imperative to "shift from an emphasis on protecting pregnant people *from* research to protecting them *through* research" (Lyerly et al., 2021). The same is true for promoting the health of lactating women and their children; clinical research must be conducted to protect lactating women and their children from the harms of breastfeeding cessation, untreated disease, and insufficiently studied medical products.

STUDY BACKGROUND

A number of domestic and international committees, working groups, and task forces have written important reports with recommendations to advance research in pregnant and lactating women (CIOMS and WHO, 2016; Hunt et al., 2017; IOM, 1994a; Manningham-Buller and Brocklehurst, 2022; NICHD, 2018; PHASES, 2020; PREVENT, 2018). Despite these

efforts and other remedies tried, such as calls for more registries, an information vacuum on dosage, safety, and efficacy of medical products in pregnant and lactating women remains. However, every report listed has recognized that legal liability and the legal context are an underexamined but potentially significant factor contributing to the reticence to move forward in this area.

In 2020, as a follow-up to its 2018 report, the PRGLAC Task Force released the *PRGLAC Report Implementation Plan*, which provided an update on the implementation of the recommendations in the PRGLAC report and provided guidance for making progress on the recommendations. The implementation plan called for the following:

> Convene a panel with specific legal, regulatory, and policy expertise to develop a framework for addressing liability issues when planning or conducting research with pregnant women and lactating women. Specifically, this panel should include individuals with legal expertise at the federal and state levels, regulatory expertise, plaintiffs' attorneys, pharmaceutical representatives with tort liability and research expertise, insurance industry representatives, federally funded researchers who work with pregnant and lactating women, and health policy experts. With agency support, the National Academies of Sciences, Engineering, and Medicine could be considered as a convenor of such a panel. (PRGLAC, 2020)

In the 2022 appropriations process, Congress mandated that NIH fund a consensus study committee "with specific legal, ethical, regulatory, and policy expertise to develop a framework for addressing medicolegal and liability issues when planning or conducting research specific to pregnant people and lactating people."[7]

COMMITTEE TASK AND APPROACH

Under the congressional mandate, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) requested that the National Academies of Sciences, Engineering, and Medicine convene an ad hoc committee of experts to conduct a study on the state of real and perceived liability around research conducted with pregnant and lactating women. The committee's statement of task is presented in Box 1-4. The committee was asked to present within this report its findings, conclusions, and recommendations for including pregnant and lactating women in clinical research while mitigating liability. The committee's findings are not identified as such and are

[7] *Consolidated Appropriations Act of 2022,* Public Law 117-103, 117th Congress (March 15, 2022).

BOX 1-4
Statement of Task

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will 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.

The committee, as a first step, will conduct data collection and analysis of the myriad of state laws and regulations governing liability for conducting research, including informed consent provisions, and to which populations they apply.

The committee will generate a matrix of the relative liability for (1) currently on-market and off-patent therapeutics and vaccines, (2) currently on-market and on-patent therapeutics and vaccines, and (3) new therapeutics and vaccines under development. This liability assessment is to address real and perceived risks to (1) private companies (e.g., vaccine manufacturers, biotech, pharmaceutical companies), (2) individual researchers and their institutions, and (3) the government for conducting research specifically on therapeutics and vaccines, including associated medical devices (e.g., diagnostic devices, drug delivery systems), for medical conditions experienced by pregnant and lactating persons. The committee will distinguish liability issues between pregnant persons and lactating persons because their liability profiles likely differ.

Based on its review of the information and other expert input, the committee will develop a report with its findings, conclusions, and recommendations for safely and ethically including pregnant and lactating persons in clinical research that substantially mitigates or avoids incurring liability (absent negligence or malfeasance). These recommendations may include:

- pre-clinical studies (e.g., reproductive toxicology studies), and different types of study design and methodologies to generate relevant evidence for decision-making;
- considerations for the treatment of obstetric/lactation conditions (e.g., pre-eclampsia, pre-term labor, mastitis) and conditions experienced during pregnancy (e.g., asthma, chronic pain);
- considerations and implications for trial participants of reproductive age who may become pregnant while enrolled in a study;
- ways to maximize the use of informed consent procedures with consideration of shared decision-making, provider-patient communication, and health literacy of trial participants; and
- potential policy changes that would address disparities in state laws and regulations while protecting research participants' legal rights and providing researchers with protection against liability.

instead woven into the narrative of this report. Conclusions represent the committee's interpretation of the available evidence and are presented at the end of Chapters 2 through 5. The committee's recommendations, which build on its findings and conclusions, are discussed in Chapter 6.

The Committee's Interpretation of the Charge

Although there are many important issues to explore in the area of research involving pregnant and lactating women, it was necessary for the committee to restrict the scope of the report owing to space and time limitations. This report primarily focuses on liability and regulatory concerns, rather than biomedical issues, issues of recruitment and retention, or communication strategies to raise the national consciousness of the issue given the charge of the statement of task. These are critical issues worth examination, and some of these topics have been addressed by the PRGLAC Task Force (NICHD, 2018), but they are outside of the scope of this committee's charge.

The committee interpreted the statement of task as asking for recommendations directly tied to liability and asking for some elements, such as different study designs, as going beyond liability. Therefore, the committee interpreted its task as examining liability and medicolegal liability issues that go beyond the narrow scope of liability. For example, Chapter 5 of the report provides an overview of factors beyond liability that prevent broader inclusion of pregnant and lactating women in clinical research. These factors are not directly tied to liability but may often get conflated with liability and are considered alongside liability in decisions whether to include pregnant and lactating women in clinical research.

The committee emphasizes the need for research on drugs and vaccines, rather than over-the-counter products. The committee also did not focus on medical devices, as examining four different regulatory and development systems (drugs, vaccines, devices, and over-the-counter products) was untenable in the given time frame.

The committee focused on liability for clinical research on general conditions that affect pregnant and lactating women. However, the committee describes in Box 1-5 its considerations for conditions that are specific to pregnant and lactating women.

The statement of task asks the committee to "generate a matrix of relative liability." The committee spent a great deal of time attempting to create such a matrix and ultimately concluded that any matrix of relative liability created would be subjective rather than based on empirical analysis, as quantifying relative liability is not possible. The committee has provided a thorough analysis of the evidence on real and perceived risks to different stakeholders; however, after careful consideration, the committee was unable to generate a matrix on relative liability. Instead, the committee did a survey of actual liability and the laws and regulations applicable to liability, all of which help to minimize harm and mitigate liability.

The statement of task charges the committee with developing recommendations "for safely and ethically including pregnant and lactating

BOX 1-5
Medical Product Development for Conditions Specific to Pregnancy and Lactation

A variety of medical conditions may arise because a woman is pregnant, including preeclampsia, gestational diabetes, severe nausea and vomiting, and preterm labor. Similarly, conditions such as mastitis, and low-milk supply may present in a woman because she is lactating. Yet, there has been little to no development of medical products to treat many of these conditions (Bahmanyar et al., 2021; Spatz, 2022).

The report primarily focuses on liability in clinical research for conditions experienced in the general population and in women during pregnancy and lactation. However, the liability considerations for research on conditions specific to pregnancy or lactation, while parallel, are distinct and compounded. First, whereas many general conditions have existing, evidence-based treatments, there is a poor understanding of the basic pathophysiology of many pregnancy- and lactation-specific conditions (Ahmed et al., 2017; Jin et al., 2024; Plows et al., 2018). Furthermore, there is no alternative to conducting clinical studies in pregnant and lactating women for products designed to exclusively serve these populations. Clinical studies must be conducted in pregnant and/or lactating women if pregnancy- or lactation-specific medical products are to get to market. However, the basic science research, the pool of obstetrical/lactation clinical investigators, and the infrastructural support that are uniquely focused on the potential problems associated with pregnancy and lactation are in short supply (Longo and Jaffe, 2008). Therefore, the forces that disincentivize clinical research in these populations effectively result in almost nonexistent innovation in this space. Only two new medications for pregnancy-specific conditions have been brought to market since 2000, and one has since been withdrawn from the market (Wicks et al., 2024). No new medications for lactation-specific conditions have been developed in that time.

Another important consideration that is likely to weigh on decisions regarding perceived liability is the potential market size for conditions specific to pregnancy and lactation. Pregnancy and lactation are temporary states, which, despite provisions made for orphan drugs, may still dissuade medical product developers from investing in treatments specific to pregnancy and lactation (Caritis and Venkataramanan, 2021).

While the focus of the report and recommendations are on addressing the lack of human data for general conditions experienced during pregnancy and lactation, the committee's recommendations also aim to address the paucity of medical products for pregnancy- and lactation-specific conditions. Careful consideration of the unique aspects of product development for these conditions is important to promote research policy and investment in this area.

persons in clinical research that substantially mitigates or avoids incurring liability (absent negligence or malfeasance)." However, negligence and malfeasance are critical components of liability, particularly in a finding of causation of a personal injury claim in a clinical trial. Therefore, the committee was not able to examine liability without consideration of negligence or malfeasance.

Study Approach

The committee comprised 14 members with expertise in obstetrics, maternal fetal medicine, pediatrics, nursing, public health, clinical research, pharmacy, law, policy, pharmacovigilance, and bioethics. Two fellows of the National Academy of Medicine also contributed to the committee's deliberations and report. The committee met six times over the course of the study to discuss and analyze the available evidence and to develop the recommendations presented in this report.

As part of its work, the committee reviewed relevant peer-reviewed literature, with the assistance of the National Academies' Research Center staff, that fell under the statement of task. Additionally, committee members submitted peer-review journal articles to study staff and the committee for consideration. While examining the literature, the committee found a robust literature on the ethics, liability, and other factors surrounding the inclusion of pregnant women in clinical research. However, the committee found substantially less literature on the inclusion of lactating women in clinical research. Therefore, the committee refers to pregnant and lactating women where the literature supports the inclusion of lactating women, but there are places in the report where the committee refers only to pregnant women. This is not to minimize the importance of including lactating women in clinical research but a result of limitations of the literature.

The committee held a public workshop in March 2020 that examined risk mitigation and liability. During this workshop, the committee heard from a defense attorney, clinical trial insurers, academic medical center counsel, an expert in institutional review boards, research participants, lawyers with expertise in tort law and compensation programs, and researchers who have experience conducting clinical studies involving pregnant and lactating women. The agenda for this workshop and the committee's other public meetings are available in Appendix A. The committee also worked with a patient advocate to collect stories of individuals' lived experience being pregnant and lactating while living with a chronic illness.

The committee contracted with law firm Hogan Lovells US LLP to conduct a review of the legal landscape of tort liability for injuries related to pregnant and lactating populations' participation in clinical trials and/or use of products regulated by FDA. This legal assessment was critical to responding to the statement of task and is referenced throughout the report; it can be found in full in Appendix B. The committee also commissioned a series of papers to inform its work. The first commissioned paper is a table of state statutes that may affect research conducting with pregnant and lactating women, which was authored by Taleena Nadkarni and Amelia Nell, law students at the University of Virginia. The full table

and their methodology can be found in Appendix C.[8] The second commissioned paper is a review of FDA regulations, guidance, and policies related to conducting research with pregnant and lactating women and was conducted by Sarah Wicks, Julie Tibbets, Elizabeth Caruso, Emily Tribulski, and Elizabeth Mulkey at the law firm Goodwin Proctor LLP. This paper heavily informed Chapter 3 of this report and can be found in full in Appendix D.[9] The third commissioned paper was an examination of the effect that the recent Supreme Court decision *Dobbs v. Jackson Women's Health Organization* may have on the legal landscape to include pregnant and lactating populations in clinical research. This paper was authored by law professor Allison Whelan at Georgia State College of Law and can be found in full in Appendix E.[10] The fourth commissioned paper was authored by the Tufts Center for the Study of Drug Development, and it was tasked with examining the successes and challenges of incentive programs and other relevant initiatives in leading to new product approvals or expanded labels for either new populations or uses (Tufts CSDD, 2023).

Defining Key Terminology

The previous work on clinical research involving pregnant and lactating women has not always been consistent in the use of terminology. Therefore, to promote clarity, the sections below provide a list of the committee's definitions for key terms used throughout the report. In addition to these terms, the committee defines any other important terminology throughout, alongside the relevant discussion. Lastly, clinical research involves many stakeholders that play different roles in developing medical products that are safe and effective for the people who use them. Box 1-6 provides an overview of the key stakeholders that are involved in conducting research with pregnant and lactating women.

Pregnant and Lactating Women

Throughout this report, the committee uses the term *pregnant and lactating women* to refer to anyone who is gestating a live pregnancy or who produces milk for a child. This terminology differs from what appears in the committee's statement of task from NICHD and in the committee's name, where this population is described as "pregnant and lactating

[8] Appendix C can be viewed online at https://nap.nationalacademies.org/catalog/27595.
[9] Appendix D can be viewed online at https://nap.nationalacademies.org/catalog/27595.
[10] Appendix E can be viewed online at https://nap.nationalacademies.org/catalog/27595.

BOX 1-6
Relevant Stakeholders and Their Roles

Clinical trial insurers: Insurance companies contract with sponsors and/or investigators to insure financial risks associated with liability and medical expenses arising out of clinical trials, such as compensation for research-related injuries to participants.

Data and safety monitoring boards (DSMBs): Independent boards monitor ongoing trials to ensure participant safety and data integrity. They can recommend modifying or stopping a trial if safety concerns arise or if it becomes clear that the intervention is effective.

Food and Drug Administration (FDA): FDA (and similar agencies in other countries) regulates and approves new medical products. FDA approves applications for clinical trials on new medical products (Investigational New Drug Application [IND], Investigational Device Exemption [IDE]), and assesses the safety, efficacy, and quality of products before they can be marketed or used widely. FDA has the authority to require collection of postmarket data for approved products.

Health care providers: Physicians, pharmacists, nurses, and other health care professionals are often involved in recruiting participants, administering treatments, and monitoring patient progress during clinical trials. Their insights and expertise contribute to the trial's success.

Industry sponsors: The research and development of pharmaceuticals and other medical products is primarily paid for by private industry. Private industry stakeholders—including pharmaceutical companies and medical device companies—conduct trials to evaluate the safety and efficacy of products and collect data to support regulatory approval.

Institutional review boards: These independent groups are responsible for reviewing and approving the ethical and scientific aspects of clinical trials. They ensure that studies protect participants' rights, safety, and well-being.

National Institutes of Health (NIH): NIH is the primary funder of basic research in biomedical sciences; this research is the foundation for identifying and developing pharmaceuticals and other medical products. NIH also provides funding for preclinical and clinical research, although the vast majority of funding for medical product research and development comes from the private sector.

Nonindustry sponsors: Some clinical trials are sponsored by nonindustry entities, including nonprofit organizations, venture capitalists, universities, and research institutions. These sponsors face some of the same risk factors as industry sponsors, while some are unique to the specific type of stakeholder.

Research participants: The most essential stakeholders are the individuals who participate in clinical trials. Their willingness to volunteer for studies helps advance medical knowledge and treatments. Their safety, informed consent, and overall experience are paramount.

Researchers and principal investigators: These are the scientists, medical professionals, and researchers who design, lead, and conduct clinical trials. They are responsible for ensuring the scientific validity, ethical standards, and safety of the study. Many of the risk factors the sponsor face are also experienced by the investigators. However, there may be unique challenges that individual investigators face when considering research with pregnant and lactating women.

persons." The latter wording was intended to recognize that not all people who become pregnant or lactate are women, such as transgender men or people who are intersex or identify as nonbinary (Kukura, 2022). People of diverse sexes (biologically determined) and genders (individual's identity) may become pregnant (Moseson et al., 2021) or produce milk (MacDonald et al., 2016).

The committee chose to use *women* to highlight the complex and highly pertinent history of discrimination against women and the impact this continues to have on their health and well-being. Discrimination against women in health care is a systemic issue that encompasses multiple aspects of medical treatment, research, access to care, and patient outcomes (Holdcroft, 2007; Paulsen, 2020). For decades, women, especially racially minoritized women in the United States, including Black, Latinx, Native American, and Asian populations, were excluded from clinical research because they might become pregnant or breastfeed their child (Bierer, 2022). Owing to systemic and structural biases and racism, racially minoritized women have faced even greater challenges with respect to inclusion and representation in clinical research. Recent policy changes have begun to correct the prolonged neglect of women's particular health conditions and needs but have not yet overcome the failure to focus on finding the appropriate dosage, safety, and efficacy of drugs during pregnancy or lactation.

Using the term *women* also aligns the report with the language in federal guidance and regulations, such as those on conducting clinical trials during pregnancy or lactation. Given how critical these documents are to the legal questions addressed in this report, linguistic consistency removes a possible source of confusion. Moreover, the analysis of the case law discussed in depth in Chapter 2 and in Appendix B found only cases involving women. When referring to pregnant or lactating women in the context of clinical care or research, the committee also uses terms such as *pregnant and lactating patients* or *pregnant and lactating research participants*. There should be no doubt, however, about the relevance and applicability of this report and its recommendations to all individuals who become pregnant or breastfeed their child, regardless of their gender identification.

Lactating

When referring to a woman producing milk for a child, this report uses the terms *breastfeeding*, *chestfeeding*, *nursing*, and *lactating*. The committee notes that human milk is provided to children in multiple ways: some children suckle directly from the breast or chest of a lactating woman, others drink pumped milk from a bottle or supplemental nursing system, some receive milk from a donor, and some are fed using a combination of human milk and infant formula. Lactation occurs naturally when a woman

has given birth and can also be induced in those who have not been pregnant; for example, some adoptive parents choose to induce lactation in order to provide their child with their own milk. The committee uses *child* or *children* throughout the report, unless regulatory guidance states otherwise, because not all breastfeeding children are infants. However, as described in Box 1-2, there are unique risk considerations for neonates and infants compared to children because of their age and size.

Patient

While most pregnant and lactating women visit a health care provider at some point during pregnancy or lactation, the committee notes that pregnant and lactating women spend a majority of their time outside of the direct supervision of a provider and make many care decisions on their own (e.g., over-the-counter medications). Thus, pregnant and lactating women are not patients merely because they are pregnant or lactating. This report generally only refers to pregnant and lactating women as *patients* when in the context of provider-based health care, or when a cited study refers to pregnant and lactating women in this way.

Clinical Research

Clinical research is a general term that encompasses several different approaches to research. For the purposes of this study, the committee has chosen a broad definition of clinical research, which includes:

- Preclinical research that uses laboratory and/or animal studies to assess safety and efficacy before testing in humans.
- Clinical studies that involve human participants can be divided into four phases:
  - Phase I: Small groups, generally of healthy volunteers, are tested to assess pharmacokinetics, pharmacodynamics, dosing, safety and activity.
  - Phase II: A larger group, generally of patients, is studied to determine efficacy and to further evaluate safety.
  - Phase III: Large-scale studies are conducted to confirm results, monitor side effects, and compare the treatment to standard treatments or placebos.
  - Phase IV: After a medical product is approved by regulatory agencies, ongoing studies monitor its long-term effects, safety, and optimal use.
- Observational studies that observe participants without intervening, often to gather information about real-world treatment outcomes, disease patterns, or risk factors.

Liability

Liability is the state of being responsible for something, especially by law. The PRGLAC Task Force report identifies liability as a significant impediment to the acquisition of an evidence base to facilitate the use of medical products by women who are or might become pregnant and by lactating women because of the fear of legal or regulatory risk or obligation for causing harm. This report does not include a definition of liability itself. For this report, the committee chose to focus on a broader concept, *legal liability risks*, which encompasses not only adverse legal decisions, but also the risks attendant to potential legal actions more generally. Even if a clinical researcher or medical product sponsor believes that it is likely to prevail in a lawsuit, the fear of becoming embroiled in such a lawsuit is likely to affect behavior. Even with favorable results, legal actions entail significant costs, including time, reputational harm, psychological harm, and legal and potential settlement fees. Throughout the report, any mention of the term *liability* refers to legal liability risks. When referring to perceived liability, the committee refers to it as such. However, addressing legal liability and minimizing harm to research participants helps address perceptions of liability. Therefore, the same strategies that mitigate legal liability also help to reduce perceived liability.

Harm and Liability

Harm and *liability* are two terms that are often conflated when discussing the factors that affect willingness to conduct research with pregnant and lactating women, but it is important to distinguish the two. *Harm* refers to injury, *liability* refers to legal responsibility for causing harm. Pregnant women may be excluded from clinical studies because of the risk of harm to them and/or their fetuses, the risk of liability for causing harm to them and/or their fetuses, or based on other factors described later in this report (see Chapter 5). It is also important to note that decisions are sometimes made based on perceptions of risk, even if those are not well founded in data or experience. In the context of this report, the committee has considered multiple different kinds of harm. There is potential harm to pregnant and lactating women and their offspring (psychological, possibly physical and economic) and harm to clinicians (psychological, possibly reputational and legal) because of the paucity of human data on which to base decisions.

Similarly, society may be harmed by the downstream effects of these injuries. There is also potential harm that may be associated with participation in clinical studies; usually these potential harms are included in informed consent as known and unknown risks. Harm may happen without liability; harms can happen even when no one has done anything

wrong. When something negative occurs, such as harm to a fetus or child, it is human nature to seek an explanation for the negative outcome (Peeters and Czapinski, 1990). That can create liability risk even when all parties have attempted to minimize harm. All of these factors are related to one another, but each must be addressed in order to develop recommendations for improving the representation of pregnant and lactating women in clinical research.

Organization of the Report

This report is organized into six chapters. Chapter 2 provides an introduction to liability, provides an overview of liability for including pregnant and lactating women in clinical studies, explores perceptions of liability, and discusses the relationship between the risk of harm and the risk of liability. Chapter 3 is about reducing the potential for harms from clinical studies with pregnant and lactating women, both through the current regulatory system and through any improvements that can be made to that system to minimize harm. Chapter 4 focuses on the mitigation of liability beyond minimizing harm, and Chapter 5 explores other factors in a medicolegal context that affect stakeholders' willingness to do research with pregnant and lactating women. Finally, Chapter 6 presents the committee recommendations and the evidence supporting each recommendation.

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2

Legal Liability

As introduced in Chapter 1, fear of legal liability arising from potential harm—to the pregnant woman and particularly to the fetus—is frequently cited as a significant obstacle to the participation of pregnant women in clinical research. It is unclear to what degree fear of legal liability related to the participation of lactating women in clinical research is thought to be a barrier to their inclusion in research, because liability concerns for lactating women are consistently cited alongside other concerns for pregnant women (Bianchi et al., 2021; Sewell et al., 2022). This chapter examines and analyzes the liability landscape related to the participation of pregnant and lactating women in the clinical research of medical products.

The generation of high-quality data is necessary to ensure that health care providers and their patients have the best possible evidence on safety, dosage, and effectiveness to treat and prevent diseases and health conditions. Society has determined that the responsible and ethical conduct of clinical research is essential to creating this evidentiary base. Sufficient data on safety and effectiveness allow the health care provider and the patient to make an informed decision about an intervention's potential benefits and the risks of harm. In the face of insufficient evidence, the health care provider and patient are in a difficult position: A decision to forgo any intervention may result in harm to the woman, their fetus, and/or their child from an untreated or unprevented condition, and a decision to use an intervention puts the patient, their fetus, and/or their child at uncertain risk of harm for uncertain benefit (Weld et al., 2022).

Many have reached the conclusion that by excluding pregnant and lactating women from clinical research, the risk of harm—to pregnant

women, lactating women, the fetus and/or child—is instead magnified and exported to the much larger clinical population (Lyerly et al., 2008; NASEM, 2023; Saenz et al., 2017). This is because once a product is approved for marketing in the general adult population, a product is eligible for use by health care providers to treat pregnant and lactating women in the clinical setting regardless of whether data on the safety, dosage, and efficacy of the product have been evaluated in pregnant or lactating populations. In other words, the risks of harm from the product have not been evaluated in the controlled and monitored setting of a clinical trial, and without the generation of high-quality data through controlled clinical trials, health care providers and pregnant and lactating women are left to experiment—with respect to safety, dosage, and effectiveness—in the clinical setting. Yet there is reason to believe that manufacturers of approved products that cause harm to pregnant and lactating women, or their fetus or child, might be shielded from liability. Manufacturers may argue that they had neither knowledge of possible risks relating to use of the product in pregnant and lactating women nor a duty to acquire such knowledge in the absence of any FDA requirement to test in these populations (American Law Institute, 2010).

Notably, the potential for legal liability is rarely discussed as an impediment to conducting clinical research in the general adult population even though all clinical research on medical products involves some risk of harm to study participants. Society has determined that research is ethically permissible provided regulatory and ethical safeguards are in place (Emanuel et al., 2008). The potential for harm is minimized through several existing oversight mechanisms, including regulatory review and approval processes, research ethics committee review of the protections for human participants (i.e., to ensure that risks are minimized and the prospect of potential benefit outweighs the risks, there is adequate informed consent, and participant selection is equitable), and where appropriate, the work of data safety monitoring boards.

Research conducted in pregnancy raises distinct risk and benefit considerations. The research may be designed to offer the potential for direct medical benefit to both the pregnant woman and fetus, to only the fetus, to only the pregnant woman, or to neither the pregnant woman or fetus. Clinical research may place either or both at risk of harm despite all efforts to minimize the potential for harm, even when one or both may benefit from the research (Kaye, 2019). It is that distinct interrelationship and uncertainty related to potential fetal morbidity and mortality that prompts liability concerns in the clinical research setting (IOM, 1994). There are also unique liability considerations related to birth injuries, which are discussed in this chapter. Assumptions about liability for potential fetal harm in the clinical research setting have led to the routine exclusion of pregnant women from clinical trial participation (Sewell

et al., 2022). Exclusion of pregnant women may occur either at the outset of the study through established exclusionary criteria or during the study because pregnancy unexpectedly occurs during research participation. The fear of potential fetal harm also is reflected in the dearth of clinical research and drug development for pregnancy-specific conditions (Fisk and Atun, 2008).

Lactating women are also excluded from clinical studies, using exclusionary criteria at the study's outset or at the level of the research agenda. Despite the fact that pregnancy and lactation are two distinct biological states, they are often conflated in the eligibility criteria of clinical trials (Van Spall, 2021). In contrast to pregnant women, where it is impossible to completely avoid any exposure to a fetus, human milk need not be given to a child if there is a concern for the safety of the child. Current Food and Drug Administration (FDA) guidance requires lactating women discontinue breastfeeding if they are administered an investigational drug as part of a clinical trial because in those cases the potential drug exposure is a research risk that has uncertain benefit to the infant (FDA, 2019). As discussed in Chapter 3, this interruption of breastfeeding is not without risk to the child. In that context, liability is not anticipated to be any greater than with the general population; the only drug exposure is to the lactating woman and yet lactating women are also frequently excluded from clinical study.

The committee's examination of civil liability includes both a review of the potential liability for harm to pregnant and lactating women and their fetus and/or child in the clinical research setting as well as the clinical setting. The term *liability* may be used colloquially to refer to any form of risk. However, liability is defined by state laws; the specific legal requirements vary from state to state. In general, a finding of civil liability requires that the individual bringing a lawsuit (the plaintiff) show (1) the defendant had a duty to the plaintiff; (2) the defendant breached their duty to the plaintiff; (3) the plaintiff suffered a cognizable harm; and (4) the breach of duty was the cause of the harm. The basis of any liability claim is harm to the plaintiff; without harm there is no case. If the harmed individual believes the harm was caused by the action or inaction of another who had a duty to prevent harm or make evident the potential for harm, the harmed individual may or may not decide to sue. Once a lawsuit is filed, the defendant may decide to settle the lawsuit before litigation begins.

Settlements do not constitute a finding of liability and frequently include statements in which the defendant denies liability. If a lawsuit does proceed to trial, the case could resolve in favor of the defendant (a finding that there is no liability), or in favor of the plaintiff, which constitutes a finding of liability. There are a number of possible outcomes if an individual is harmed in clinical research, many of which will not result in liability.

The risk of liability and its potential costs is a factor that is considered among many in decisions about whether to conduct clinical research.

The committee's statement of task asks for an examination of the state of "real and perceived liability around research conducted in pregnant and lactating persons." The committee interprets "real" liability to mean evidence of legal cases that resulted in a legal opinion in addition to those that resulted in a settlement. A literal reading of the term *liability* would be limited to a formal finding by the court in favor of the injured party. In considering *legal liability risks*, the committee includes settlements in its interpretation to also include an examination of published cases and other reports that reveal the breadth of litigation surrounding a particular product that does not assign responsibility for alleged harm to a defendant. This includes cases deciding in favor of the defendant, settlements, the formation of multidistrict litigation, and other litigation-related activity.

A SURVEY OF REPORTED LEGAL LIABILITY RISK

A search of the literature revealed no existing survey on the legal liability risk associated with medical products researched in, and dispensed to, pregnant and lactating women. The committee therefore commissioned lawyers from the law firm Hogan Lovells US LLP to conduct such a survey (see Appendix B for full survey). The requested search was designed to capture all potential case law related to drugs, biologics, or medical devices studied in or used by pregnant or lactating populations. A description of their search methodology and a detailed reporting of results can be found in Appendix B. A brief summary of the results is presented below, followed by a discussion of the committee's insights. As noted in the discussion, any claims of injury may be resolved privately without litigation through a claims process or discussion with the investigator, study site, or the sponsor of the clinical trial. These settlements are usually not made public, and therefore, the survey provided is an informative, yet incomplete picture of actions resulting from an alleged injury.

Overview of Findings

As discussed below, the survey reveals no reported legal cases involving liability related to a pregnant woman's participation in a clinical study, at least since the development of formal regulations for clinical research in 1963. However, the survey unveiled a considerable number of cases involving liability related to a pregnant woman's postmarketing use of medical products. The survey also found no cases relating to a lactating woman's participation in a clinical trial, although it did find a number of cases involving lactating women's postmarketing use of one product.

Liability for Pregnant Women's Participation in Clinical Research

The search did not identify any reported cases alleging injuries based on the administration of an investigational medical product to a pregnant woman after FDA adopted regulations governing clinical research in 1963; no reported cases raise legal claims alleging injury resulting from participation of pregnant women in a clinical study.

There have been reported cases brought on behalf of children whose mothers participated in Richardson Merrell's study of Kevadon (thalidomide) in the 1950s and1960s—in reality, the unapproved drug was distributed for marketing purposes without legitimate investigatory use, explained in Box 2-1 (Vanderbes, 2023). Similarly, cases have been brought for long-tail effects of clinical trials involving diethylstilbestrol (DES), but again, the clinical trials themselves took place in the 1960s before modern FDA regulations were promulgated.[1,2] In addition, a case was brought under the False Claims Act against a sponsor (Pfizer) of a COVID-19 vaccine for protocol violations, including the administration of the vaccine/placebo to pregnant women. No injuries were alleged in that case, though an appeal is pending.[3]

Postmarketing Liability for Pregnant Women

In contrast to the dearth of legal cases in the clinical research setting, there are over 1,000 filed cases associated with pregnant women's postmarketing use of medical products, both on-label and off-label, involving products prescribed for pregnancy-related conditions (e.g., Zofran—morning sickness) and for general conditions nonspecific to pregnancy (e.g., Zoloft—antidepressant). The case law search revealed liability claims against 36 unique FDA-approved products being used by pregnant women in the clinical setting, excluding claims against DES. Those cases were typically brought against the developer of the product or the generic drug manufacturers or distributors (in the case of drugs that are off-patent). Less frequently, cases were also brought against the health care providers (and the associated medical system) who had prescribed the therapy. Parental injuries alleged were limited to emotional distress.

Most of the cases involving pregnant women's use of postmarketing medical therapies involved birth anomalies in the infant that were apparent at birth. Some of these cases, however, involved fetal harm that

[1] Wetherill v. University of Chicago, 570 F.Supp.1124 (N.D. Ill. 1983).

[2] *Mink v. University of Chicago,* 460 F.Supp.713 (N.D. Ill. 1978).

[3] *United States of America ex rel. Brooks Jackson v. Ventavia Research Group, LLC. Et al.,* No. 1:2021cv00008 (E.D. Tex. 2023).

only became apparent considerably later after birth. For example, a case that may potentially involve thousands of litigants alleges that children's attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders are caused by in utero ingestion of acetaminophen—though a judge recently ruled that the plaintiffs' evidence was inadmissible.[4] In the case of DES, claims of injury to subsequent generations have been made, and actions relating to drugs that were ingested decades previously continue to be filed. Some drugs have been the subject of large numbers of claims involving hundreds or even thousands of cases.

Liability for Lactating Women's Participation in Clinical Research

There are no reported legal cases related to a lactating woman's use of an investigational medical product in the clinical research setting.

Postmarketing Liability for Lactating Women

No cases were identified involving injury to a child caused by a medical product used by a lactating woman. The reported cases that involve postmarketing liability for lactating women all involved a single drug for use in lactation, bromocriptine (Parlodel), a lactation inhibitor, and all of those cases alleged injury to the mother (e.g., stroke and seizure). Parlodel is no longer indicated for lactation inhibition.

Discussion of the Case Survey Data

Several conclusions may be drawn with a reasonable degree of confidence based on the available data and general knowledge regarding the regulatory context and litigation involving medical products. In the most conservative interpretation, there is limited liability risk relating to the use of medical products in lactating women either in clinical research or through the use of approved medical products on the market. There is little liability risk relating to the use of medical products by pregnant women in clinical trials. There *is* evidence of liability risk relating to pregnant women's use of approved medical products on the market, and there is some evidence that some aspects of that liability might be obviated by clinical trials in pregnant women.

For several reasons, even with the more expansive view of legal risk used by the committee in its analysis, this review offers an informative,

[4] *In re Acetaminophen – ASD – ADHD Prods. Liab. Litig. In re Acetaminophen - ASD-ADHD Prods. Liab. Litig.,* 22md3043 (DLC) (S.D.N.Y. Apr. 27, 2023).

yet unavoidably incomplete picture of actions initiated as a result of alleged injury. First, not all filed cases result in published written opinions. For example, opinions of state trial courts usually are not reported nor are claims that are settled out of court. Second, there is very little transparency in the civil justice system, including no systematic information on how many cases go to trial in federal court, so there is no information on how many legal actions have been filed (Saks, 1992). The committee also has no way to determine how many pregnant or lactating women have participated in clinical research to understand the extent to which the inability to find evidence of liability in clinical research is caused by there being few trials that enroll pregnant and lactating women; ClinicalTrials.gov does not appear to have the necessary search criteria. Although *pregnancy* and *lactation* are searchable conditions in ClinicalTrials.gov, the results are both overinclusive and underinclusive. For example, using *pregnancy* as the search condition displays every trial that mentions the word *pregnancy*, including *not pregnant*. However, this search does not show trials that include pregnant women but are not treating conditions specific to pregnancy.

Further, for the trials that do appear in the search, inclusion and exclusion criteria may not be reported and results may not be reported by whether participants are pregnant or lactating. Similarly, although there are rough estimates of percentages of pregnant women who use medical products during pregnancy, there is no comprehensive reporting on how many pregnant women use those products or in what combinations. Nonetheless, this effort has produced a general profile of the landscape of legal liability relating to pregnant and lactating women's use of medical products.

Limited Presence of Liability in Clinical Research

The committee's review suggests that the risk of liability resulting from the use of investigational products by pregnant women and lactating women is currently substantially less than the risk of liability from the use of marketed drugs by pregnant women and lactating women outside of the clinical research context. The limited liability for clinical research involving these populations is likely attributable to multiple factors.

General Factors

First, there are currently few clinical trials that include pregnant or lactating women as participants relative to the number of clinical trials being conducted generally. For example, of the actively recruiting NIH-funded Phase III and IV trials reported in clinicaltrials.gov as of

2022, 69 percent excluded pregnant participants and 50 percent excluded lactating participants (Thiele, 2022). However, given the incomplete reporting of inclusion and exclusion criteria, the percentage of trials that exclude pregnant and lactating women is likely much higher (Smith, 2020). As a result, if the total number of pregnant and lactating trial participants is low, the number of adverse events is also expected to be quite low. That means that there is likely to be limited litigation since there will be fewer instances of injuries for which compensation can be sought.

Second, in all medical research contexts, a much smaller number of people use a medical product in clinical research studies compared to general use in ordinary medical practice following FDA approval for marketing. That number is only gradually increased as a medical product proceeds through the phased research process required under FDA regulations. A late-phase trial for a drug, Phase III, typically includes only 300 to 3,000 participants; a Phase III trial for an orphan indication would include far fewer people. Even trials for therapies indicated for a very broad population (e.g., vaccines) typically include only tens of thousands of participants, while the therapy may be used by millions. The more people that use any therapy, the more likely it is that there will be adverse events. Some of those may be attributable to background risk, and others may be caused by the rarer effects of the drug that only occur in particular populations.

There are also aspects of clinical research that make lawsuits less likely to be filed, and if filed, to succeed, than other medical liability cases. Those factors continue to hold true even though there was an uptick in the number of clinical research claims (that did not involve pregnant and lactating women) filed in the late 1990s and early 2000s (Mello et al., 2003).

The vast majority of clinical research is subject to extensive regulatory oversight to ensure that the rights and welfare of human participants are protected. The research is reviewed by institutional review boards (IRBs) to ensure that informed consent is appropriate, risk is minimized, benefits and risks are appropriately balanced, and that participant selection is equitable.

Clinical studies usually also have rigorous inclusion and exclusion criteria that are designed to limit the likelihood of adverse events. In addition, participants in clinical studies are typically monitored more closely than patients in ordinary medical practice. The comprehensive nature of informed consent processes in clinical research, including documentation requirements, may be a factor that limits the likelihood of harm and ensuing litigation in the clinical trial context. Indeed, in the medical context, while surgery usually requires documentation, much prescription of drugs in medical practice is done without much discussion or any documentation. In contrast, current federal regulations require that informed consent for clinical trials be fully documented identifying the prospect of medical

benefit as well as potential risks posed to the participant and the fetus or child, including that those potential risks be updated regularly as adverse events are detected. It is important to emphasize that in the context of clinical trials, informed consent does not create an "assumption of risk" defense that might bar any claims by a participant, even if the risks were unreasonable. Instead, the informed consent provides information about potential risks and the federal regulations require that those risks be reasonable.

Finally, the federal human subject protection regulations require that the informed consent indicate whether compensation for research-related injuries is available, but they do not require that such compensation be provided. Nonetheless, several institutions provide compensated medical care for research injuries and a few institutions provide broader compensation for research injuries (Resnik et al., 2014). Such compensation for research-related injuries and related care may also limit interest in litigation (Mariner, 1994).

All of this, however, does not negate the overall finding from this survey. There have been no reported cases based on injuries to pregnant or lactating participants in clinical trials since the 1963 promulgation of FDA investigational drug regulations. This would indicate that evidence of legal liability risk is not the driver of reticence in including pregnant and lactating women in clinical research.

While a thorough analysis of liability for conducting research with pregnant and lactating women in the international context was beyond the scope of this report, the committee's findings of limited liability for including pregnant and lactating women in clinical trials do merit a comparison to other countries. There are notable differences between U.S. tort law and the systems of tort law in other countries. For example, punitive damages are rewarded less frequently in European countries than in the United States, though they are also uncommon in the United States (Koziol, 2015). U.S. tort law also relies more heavily on jury-determined awards, which tend to be higher than those determined by a judge, than in Europe. Perhaps most importantly, clinical trials conducted in European Union member states are required to obtain insurance to cover compensation for research-related injuries.[5] Yet pregnant and lactating women are also routinely excluded from clinical studies in European countries despite the greater protections from liability in comparison to the United States (Nooney et al., 2021). This supports the notion that legal liability is not a primary reason that pregnant and lactating women are excluded from clinical studies in the United States.

[5] *Clinical Trials on Medicinal Products for Human Use*, Regulation EU No 536/2014 (Apr. 16, 2014).

Considerations Specific to Lactation

Under current FDA guidance, an infant would not be fed human milk during a clinical lactation study unless the lactating mother was already taking a medication and breastfeeding prior to enrollment in a clinical study. Therefore, the risk of liability resulting from the use of investigational medical products in clinical lactation studies will likely be limited to injuries to the lactating woman.

Liability Associated with the Use of Postmarketed Products

As the case law demonstrates, there are legal liability risks to the use of medical products by pregnant and lactating women in the postmarketing setting. Interestingly, there is arguably a scenario in which conducting clinical research in pregnant and lactating women could generate additional liability for the use of medical products in the clinical setting.[6]

Considerations Specific to Pregnancy

It is not surprising that most of the cases involving injuries alleged to have been caused by in utero exposure to marketed medical products involve birth anomalies. Although there is an approximately 3 percent background risk of serious birth anomalies with every pregnancy (March of Dimes, 2019), that level of background risk is not well known by the public and may vary by population (Petersen et al., 2015). It is possible that fetal harm temporally associated with in utero exposure to a medical product will be attributed to that medical product. This is not enough by itself to establish causation, but it does increase the risk of litigation. In fact, that is what happened with pyridoxine/doxylamine (Bendectin), a drug that was approved for morning sickness and prescribed to more than 30 million people between 1956 and 1983 when it was voluntarily withdrawn from the market by the manufacturer (Green, 1996; Lee and Saha, 2013).

No causal link between Bendectin and birth anomalies was ever scientifically established, but the high cost of litigation still led the drug's sponsor to remove it from the market (Goldberg, 1996). While a typical defense against a liability claim related to the use of a medical product might argue that the harm was caused by factors not related to the product (e.g., smoking, drinking, physical activity, medical history), such a defense would be difficult to mount in the context of fetal injuries because of relatively fewer potential alternative causation factors in comparison

[6] As presented to the committee in open session by John Beisner on March 23, 2023.

to adults.[7] Along similar lines, analyzing clinical trial results in smaller subpopulations, such as pregnant and lactating women, may lead to a false finding of a safety signal, since the randomization of the full data set is not preserved (EMA, 2019). This false finding could potentially cause liability in the postmarketing setting both for use in pregnant and lactating women and to cast doubt on the overall safety profile of a product. At the same time, the thalidomide story, and its associations with corporate malfeasance, is relatively well known (see Box 2-1). This could present a greater risk that a jury would find liability and award higher damages than in many other cases.

An additional characteristic that contributes to the legal risks inherent in the use of marketed medical products by pregnant women is the potential for long-tail effects. In drug liability cases, long-tail claims involve latent bodily injury that becomes apparent only many years after the alleged harm-causing conduct occurred. The DES cases provide an example of particularly extended long-tail effects, manifesting even in the next generation (Box 2-1). Because long-tail claims often involve hundreds of claimants, "in part because it is easier to spot a pattern emerging when there is a larger number of parties suffering the same kind of harm," they pose significant liability risks (Appendix B). The long-tail risks also present challenges for conducting trials to properly assess these risks. To identify a potential long-term, relatively rare effect would require conducting a decades-long clinical trial with thousands of patients to generate enough data for a signal. This presents challenges with participant retention, false safety signals, and false negative results. Therefore, real-world evidence collection once the product is on the market is likely the only way to identify long-tail effects (see Chapter 3 for a more thorough discussion of postmarketing commitments).

Drug manufacturers might face liability for a defective product or a failure to warn if postmarketing experience indicates that the drug is more dangerous or less effective for women and the company failed to test the product in women (Flannery and Greenberg, 1994). The manufacturer of a drug that was "in widespread use while its teratogenic effects were 'unknown but knowable'. . . might harm many children, and their lawyers may argue that the manufacturer had a duty to find out about these effects" (Clayton, 1994). The potential for liability could be increased to the extent that the manufacturer encouraged use of the drug by or marketed the drug to pregnant and lactating women, such as by promoting it to OB-GYNs. These ideas are captured in the *Restatement of the Law (Third) of Torts* that provides that medical product "manufacturers have the responsibility to perform reasonable testing prior to marketing

[7] As presented to the committee in open session by John Beisner on March 23, 2023.

BOX 2-1
The Long Shadow of Thalidomide and DES

The willingness to include pregnant women in clinical research is heavily influenced by a few high-profile examples where medication use during pregnancy caused a significant amount of harm to the fetus in utero, including thalidomide and diethylstilbestrol (DES). However, neither of these drugs were subject to modern drug evaluation processes, and the trials that did take place were not conducted using current standards. Had appropriate preclinical and Phase I studies been done according to modern standards, those studies would have likely revealed that thalidomide was dangerous for pregnant women and their fetuses and that DES was not effective for preventing adverse pregnancy outcomes (Botting, 2015).

Thalidomide was developed in 1950 by the German company Chemie Grünenthal. It was originally developed to be a sedative without the negative side effects of barbiturates. However, its use quickly expanded to treat additional conditions, including nausea and morning sickness during pregnancy. Thalidomide's main selling point was its apparent safety; Grünenthal claimed that it was impossible to give animals a lethal dose of the drug, a claim it made based on an LD_{50} test. The drug was never tested in pregnant animals, and teratogenic potential was never evaluated prior to use in humans.

Following the over-the-counter licensing of thalidomide in Germany in 1956 (under the name Contergan), the drug was licensed for production by pharmaceutical companies around the world. In the United States, the William S. Merrel Company applied for marketing approval from FDA. However, thalidomide was not approved by FDA because of the lack of safety data. While the drug was awaiting approval, Merrel was handing out samples of the drug to clinicians for alleged investigational purposes, which were given to more than 20,000 Americans, about 600 of whom were pregnant. However, these "studies" were intended to create marketing demand for the drug, not to conduct research, and patients were not asked for their consent, monitored, or tracked.

Because patients were not tracked in trials, it took 5 years after thalidomide was on the market for researchers to discover the connection between the drug and babies born with multiple malformations, most notably shortened "seal like" limbs known as phocomelia. Thalidomide can cause serious impairments when taken in early pregnancy, and even one tablet is enough to cause significant impairments during pregnancy. It is estimated that over 10,000 babies worldwide were born with malformations caused by the drug.

Diethylstilbestrol (DES) is an artificial hormone that was introduced for a variety of indications in 1939. It was never patented and therefore was synthesized by several different pharmaceutical companies. DES received FDA approval in 1941 for a number of uses, and the indication was expanded in 1947 to prevent adverse pregnancy outcomes. From 1940 to 1971, DES was given to pregnant women to prevent miscarriage, premature labor, and related complications of pregnancy.

DES use declined in the 1950s, after a double-blind clinical trial assessing pregnancy outcomes of women who received DES showed no benefit of taking DES in pregnancy. However, DES continued to be prescribed for use in pregnant women throughout the 1960s.

BOX 2-1 Continued

In 1971, a study was published linking DES with vaginal clear cell carcinoma for children who had been exposed to DES in utero. FDA notified health care providers that DES should not be prescribed for use in pregnancy following the publication of this study and added pregnancy as a contraindication to the drug label. Females exposed to DES in utero, also known as DES daughters, are at an increased risk for several cancers, including clear cell adenocarcinoma, breast cancer, pancreatic cancer, and cervical precancers. The increased risk of developing many of these cancers is elevated even for DES daughters in their 40s and 50s, meaning that although DES has been contraindicated in pregnancy since the 1970s, claims of harm from DES continue to emerge. Due to the length of follow-up that would have been needed to identify that risk to females exposed in utero, appropriately conducted clinical trials likely would not have identified these injuries. However, appropriately conducted clinical trials would have revealed that DES was not effective to prevent adverse pregnancy outcomes and therefore would not have been prescribed to the extent it was.

SOURCES: NIC, 2021; Vanderbes, 2023; Zamora-León, 2021.

a product and to discover risk and risk-avoidance measures that such testing would reveal." The committee looked for evidence of those arguments in the case law data. There is evidence of claims that include those arguments; for example, plaintiffs in the Paxil and Zofran cases did allege a failure to conduct studies about pregnancy risks.

PERCEIVED LIABILITY

Because the examination of legal liability risks associated with the participation of pregnant and lactating women in clinical research revealed little evidence of such risks, the committee then considered the potential drivers for the perception of liability. First, it is important to note that the disconnection between actual liability and people's perceptions of liability is not unique to research with pregnant and lactating women. IRBs are more likely to focus on the potential magnitude of harm than the likelihood of that harm taking place, thus overestimating the risk (NRC, 2014). Physicians have a distorted notion of the likelihood of malpractice liability (Engstrom, 2014). Fear of liability seems to exist in uncertainty; the exact contours of that liability, how liability interacts with harms, and what factors exacerbate the likelihood of liability are not well understood by many of the actors involved in clinical research (Mastroianni et al., 2017). The fact that potential harms attendant to research with a pregnant woman may also involve a fetus who cannot consent likely worsens this uncertainty.

There may also be a conflation of risks generally already associated with pregnancy; obstetricians face among the highest rates of malpractice cases (Sakala et al., 2013). In addition, the terrible experience of thalidomide and DES inevitably colors the decision making involved. Although the harm resulting from the thalidomide event is actually an argument for the inclusion of pregnant women in research, and likely would have been obviated if current research standards had been required, these events provide a stark, well-known narrative with graphic images of what has gone wrong in the past.

Perceptions of liability involving lactating women are perhaps more perplexing. While a lactating woman is certainly scientifically complex, the liability concerns that extend to research with pregnant women are not present because any potential risks in the research context are generally borne by the lactating woman. A child can be fed the milk of a lactating woman who is using a medical product in a clinical research study, but only when the lactating individual had already chosen to use the medical product independent of the research. Indeed, the U.S. Department of Health and Human Services (HHS) human subjects regulations applicable to pregnant women, discussed in detail in Chapter 3, do not apply to lactating women.[8] It is possible that people simply view lactating women as part of a continuum from potentially pregnant to lactating and fail to disaggregate the different risks that are present at each stage. Regardless of the reason, conflating pregnant and lactating women does harm to lactating women by associating them with liability risk that evidence does not support.

Finally, too much focus on liability risks makes it easier to imagine harms that might be associated with inclusion in clinical research, but this ignores the risks of harms that might be associated with not doing the research. Although it may seem counterintuitive, harms that result from omission of activity may exceed the harms from commission of activity. Thus, it feels safer to avoid interventions with pregnant and lactating women than it does to conduct research with these populations. This feeling is often based on scant evidence and speculation (Baylis and Ballantyne, 2016). Risk assessment is already one of the most challenging aspects of medical research and treatment, and there is evidence that in the context of pregnant women, that assessment is rife with the influence of cognitive biases (Lyerly et al., 2009). There appears to be a widespread cultural significance to any potential risk to the fetus that neglects to acknowledge the high degree to which the health of the pregnant woman

[8] *Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,* 45 CFR 46 66 FR 56778.

and that of the fetus are intertwined (Lyerly et al., 2008). This combination of cultural reticence toward fetal risk and lack of understanding of relative risk may make sponsors, clinicians, IRBs, and pregnant women assume that research is the riskier proposition when in fact it may be the best way to reduce harm for both pregnant women and the fetuses (Minkoff and Marshall, 2016).

LAW AND LIABILITY IN CLINICAL RESEARCH

The statement of task asks the committee to conduct data collection and analysis of federal and state laws and regulations governing liability for conducting research. While the committee has found very limited indications of legal liability risk in the context of clinical research with pregnant and lactating women, it is useful to understand the contours of that potential liability both to reduce uncertainty and to mitigate potential future liability, especially if clinical research involving pregnant and lactating women is to be expanded.

Stakeholders

Legal liability for research relating to the use of an investigational product by pregnant and lactating women involves medical product companies and other research sponsors (e.g., contract research organizations), research institutions, IRBs, clinical investigators, and potentially in some states, the pregnant or lactating participants themselves if their participation in clinical research could be considered negligence. Separately, there is potential criminal liability for pregnant women, which is discussed later in this chapter. The government is not usually at risk for legal liability in such contexts owing to principles of sovereign immunity. An exception is where the Federal Tort Claims Act (FTCA) provides an exception to sovereign immunity for the direct actions of federal employees within the scope of their employment. That exception may be applicable to vaccine contexts that are quite different and are described separately below.

Theories of Legal Liability

The types of injuries that could give rise to potential claims of legal liability are similar for injuries related to both clinical research and marketed products and include harm suffered directly by a pregnant or lactating woman, harm to a fetus or child who was exposed to the drug in utero or through human milk—respectively, and harm to subsequent generations resulting from pregnant and lactating women's drug exposure or fetal or breastfed child drug exposures (long-tail effects). Box 2-2 defines

BOX 2-2
Theories of Liability: Terms and Definitions

Strict liability: A defendant is liable for harm caused, regardless of the defendant's knowledge of the defect or intent.

Negligence: A defendant is liable for harm caused if the defendant failed to behave with the level of care that a reasonable person would have exercised under the same circumstances. Negligence may be attributable to the defendant's actions or failure to act when defendant had a duty to act.

Product liability: A defendant is liable if a defective product caused the plaintiff's injury. A product defect may be caused by a strict form (manufacturing defects, deviation from design specifications) or a form more akin to negligence (design is deemed unreasonably dangerous).

Breach of warranty: A defendant is liable if there is a violation of an express or implied contract of warranty that causes harm; for example, if a seller expressly or implicitly assures a buyer about the quality of a product and that assurance is proven untrue.

Inadequate informed consent: A defendant is liable if defendant breaches the duty to provide what a reasonable individual would want to know about the risks and benefits of care and harm results; defendant has a duty to provide complete and accurate information in such a way that the individual can understand.

Failure to warn: A defendant is liable if a plaintiff is injured because of a failure to convey information that users need to use the product safely, such as instructions for use and warnings about potential risks.

Medical malpractice: A defendant is liable if the defendant breaches their professional duty to a patient by failing to follow professional standards of care, and this breach causes harm.

terms for theories of legal liability. The legal bases for liability for injury resulting from research involving pregnant and lactating women are no different than the bases for any claim that arises in the context of clinical research generally. These claims arise under state law, mostly as torts, and include product liability, strict liability, breach of warranty, negligence, inadequate informed consent, failure to warn, and medical malpractice. Because these claims arise under state law, there may be variations in legal requirements that can have important consequences for the viability of any claim. Nonetheless, under any theory of liability, the plaintiff must establish that the defendant breached a legal duty and that the breach caused harm. At a minimum, the plaintiff must demonstrate through competent scientific evidence that the research caused the alleged injury. While the elements of causes of action for personal injury vary from state to state, in general, the plaintiff must show that the defendant failed to warn of a risk that the defendant knew or should have known of or that the defendant failed to meet an applicable standard of professional care.

Causation is a core element of a personal injury claim; even if the plaintiff can prove that the defendant acted negligently in a clinical study or failed to provide adequate warnings of risk, the plaintiff must still show that the defendant's actions were among the proximate causes of their injuries (DeBoy and Wang, 2020). To prove causation, plaintiffs may be required to present expert testimony that explains the scientific merits of their claims, and defendants will usually present expert testimony that counters those claims. The standard under which courts are to evaluate scientific expert testimony was actually created in one of the Bendectin cases. In *Daubert v. Merrell Dow Pharmaceuticals*,[9] the Supreme Court ruled that to admit scientific expert opinion into evidence, courts must examine the experts' methodology to ensure scientific validity. Nonetheless, despite these efforts to improve the standards for admissibility of scientific evidence, this process continues to be fraught with uncertainty for both plaintiffs and defendants.

Damages for torts relating to clinical research include compensation for lost wages and for medical and other expenses, damages for pain and suffering, and punitive damages for particularly egregious violations. In cases involving congenital anomalies or permanent harm caused during delivery, expenses for a lifetime of care may be very substantial. Punitive damages may also be in play in egregious cases or where fraud is involved (Mello et al., 2003).

Clinical research is fundamentally different from medical practice in that the core function is not to treat the patient (although therapeutic trials do confer a potential for direct medical benefit to the pregnant or lactating woman, fetus, and child), but rather to deliver generalizable scientific knowledge. Clinical research litigation is also a relatively new and rare phenomenon, and there are limited cases from which to glean information about the relative duties of the various stakeholders and how legal principles applicable to medical product liability generally may apply.

Potential Liability for Sponsors

Courts have had different responses to what duties a medical product sponsor may owe a participant injured in a clinical trial (DeBoy and Wang, 2020). Several courts have found that the sponsor owes no legal duty to the participant because sponsors have limited, if any, contact with the participant.[10] Instead, it is the duty of the clinical investigator and the IRB to protect the participant (Feehan and Garcia-Diaz, 2020; White, 2020). Other courts have found that the sponsor may have, at a minimum, duties

[9] *Daubert v. Merrell Dow Pharmaceuticals*, 09 U.S. 579 (1993).
[10] *Wholey v. Amgen, Inc.*, 165 A.D.3d 458 (N.Y. App. Div. 2018).

to ensure that clinical research protocols protect participants' safety, that potential risks are appropriately conveyed to clinical investigators, and that appropriate mechanisms (e.g., data safety monitoring boards) are in place to coordinate and identify safety signals (DeBoy and Wang, 2020).[11,12,13,14]

Relatedly, there is no consensus among legal scholars about the applicability of the learned intermediary doctrine to clinical research liability actions. The learned intermediary doctrine, which is relevant to a claim based on a failure to warn, holds that a manufacturer of prescription medications or medical devices has a duty to advise the prescribing medical professional of the proper use and potential risks of its products, rather than a duty to advise the patient or the public (American Law Institute, 2010). In the clinical setting, if a patient suffers an injury from a prescription medication, the learned intermediary doctrine might shield the manufacturer from liability, which is passed down to the prescriber. There is no consensus among states as to the source or the scope of the learned intermediary doctrine as a defense, although every state now acknowledges the defense in some form (McQuain, 2018). A number of courts have indicated that the learned intermediary doctrine may apply to clinical research products liabilities claims in the same way that it applies to cases involving products already on the market, but there are not enough cases to determine that definitively (DeBoy and Wang, 2020).[15,16] In addition, if the information provided to the clinical investigator for the informed consent does not match information held by the sponsor, the learned intermediary doctrine may not apply.[17]

Finally, it is unclear how preemption doctrine may work to insulate a medical product sponsor from liability for failure to warn in a clinical research context. The theory of a preemption defense is that a manufacturer cannot be liable for injuries caused by a failure to warn if the applicable warnings were approved by FDA (Grossi and O'Connor, 2023). However, in *Butler v. Juno Therapeutics*, the manufacturer tried to claim that the plaintiffs' state law claims were preempted because the study was subject to an investigational new drug application (IND) issued by FDA. The court rejected that claim because preemption claims are dependent on FDA's approval of a product and a product's label. Such a claim may be stronger if a clinical study involves an approved drug in a postmarketing

[11] *Kernke v. Menninger Clinic,* 172 F. Supp 2d 1347 (D. Kan. 2001).
[12] *Zeman v. Williams,* CIVIL ACTION NO. 11-10204-GAO (D. Mass. Feb. 4,2015).
[13] *Liu v. Janssen Research & Dec., LLC,* B269318 (Cal. Ct. App. Jan. 3,2018).
[14] *Butler v. Juno Therapeutics,* 541 F. Supp. 3d 774 (S.D. Tex. 2021).
[15] *Kernke v. The Menninger Clinic,* 173 F. Supp. 2d 1117, 1121 (D. Kan. 2001).
[16] *Tracy v. Merrell Dow Pharmaceuticals,* 569 N.E.2d 875, 878–80 (Ohio 1991).
[17] *Butler v. Juno Therapeutics,* 541 F. Supp. 3d 774 (S.D. Tex. 2021).

study.[18] A complication to these claims is that a product's patent status can influence the success of such an argument. While generic drug holders and medical device manufacturers may avail themselves of such a defense, medical product sponsors whose drug is still on patent must show there was "clear evidence" FDA would not have approved the labeling change the plaintiff claims was needed to prevent his or her injury in order to avoid liability.[19]

Potential Liability for Researchers and Research Institutions

Questions surrounding the duties and liability of clinical researchers and their research institutions are also complex. At a minimum, investigators are required to obtain a valid informed consent from study participants, and investigators must also fulfill various duties. These include the duty to adhere to the applicable standard of care and a duty to reasonably protect the participant's safety by adhering to the protocol and human subjects research regulations (DeBoy and Wang, 2020). Investigators may have conflicting interests as both researchers and health care providers, and research may involve procedures that are not in the patient's best interests (Shepherd and Riley, 2012). In the context of the research, the applicable standard of care is set by regulation and by what a "reasonable" IRB would require (Mello et al., 2003). Research institutions are responsible for overseeing the activities of their affiliated investigators and may be responsible for overseeing the applicable IRB. In all of this, they are bound by human subjects regulations to protect the safety of research participants, and failure to meet those requirements could threaten their larger research enterprise.

IRBs, contract research organizations, and data safety monitoring boards all have duties to provide safety oversight. IRBs have significantly more duties, including reviewing informed consent, determining an acceptable risk–benefit ratio for the research, reviewing the research design and protocols, and assuring and monitoring the safety and welfare of participants (DeBoy and Wang, 2020). In its review, the IRB must also consider risks to especially vulnerable populations and the influence of any potential conflict of interest (Mello et al., 2003). IRBs were not originally a focus of drug-liability claims, even when clinical trials were involved, but creative claims by plaintiff's lawyers since the 1990s have greatly increased their exposure (Mello et al., 2003).

As is made clear above, the duties involved in clinical trial litigation hew closely to the regulations surrounding human subjects research.

[18] *Murthy v. Abbott Labs.,* CIVIL ACTION NO. 4:11-cv-105 (S.D. Tex. Mar. 6, 2012).
[19] *Wyeth v. Levine,* 555 U.S. 555 (2009).

Federal regulations govern the conduct of most clinical trials in the United States. Most research institutions commit to abide by the Federal Policy for the Protection of Human Subjects, which is known as the Common Rule, because it is codified in separate regulations by each of its 15 federal agency and department signatories.[20,21] The Common Rule is administered by HHS and addresses IRB review and approval of research protocols and other ethics protections for human research participants, such as informed consent, risk–benefit assessment, and the equitable selection of participants. Research conducted as part of FDA's premarket review is governed by FDA's regulations, which are very similar although not identical to the Common Rule. FDA's regulations appear in two parts, rules for IRBs and rules that govern informed consent.[22,23]

HHS has specific regulations that apply to research supported or conducted by HHS with pregnant women (Subpart B),[24] but there are none for lactating women. Although FDA does not have specific regulations for pregnant women, it has issued draft guidance for both pregnant and lactating populations (FDA, 2018). Draft guidance, and guidance documents generally, are not legally binding but are usually followed closely by industry (Seiguer and Smith, 2005). FDA-regulated research with pregnant or lactating women that is conducted or supported by HHS is subject to both FDA and HHS regulations and guidance.

In addition, a number of states have laws that may apply to research involving pregnant and lactating women (Appendix C).[25] Generally, these include laws concerning the permissibility of fetal research, laws that grant the designation of personhood to a fetus, and laws that interpret child abuse and substance abuse during pregnancy or lactation. The specifics of the laws vary from state to state, and not every state has a relevant statute that could apply to research involving pregnant and lactating women.

A number of fetal personhood statutes went into effect after the U.S. Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* (Guttmacher Institute, 2023). In a growing number of states, prosecutors have brought actions for fetal endangerment against pregnant women who have used illegal drugs. Since many research studies include routine

[20] Federal Policy for the Protection of Human Subjects, 82 Federal Register 7149-7274 (Jan. 19, 2017).

[21] The HHS version of the Common Rule, for example, is codified at 45 CFR part 46, Subpart A.

[22] *Institutional Review Boards,* 21 C.F.R. Part 56.

[23] *Protection of Human Subjects,* 21 C.F.R. Part 50.

[24] *Subpart B – Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,* 45 CFR Part 46.

[25] Appendix C can be viewed online at https://nap.nationalacademies.org/catalog/27595.

toxicology testing, this could pose an increased risk for some pregnant participants and privacy protections will be needed. Even more troubling, there have been increased prosecutions alleging fetal endangerment against women who have experienced pregnancy losses through miscarriage or stillbirth. While the courts in most states have overturned convictions relating to charges of fetal endangerment (only the supreme courts in Alabama and South Carolina upheld convictions), in some states it has not slowed prosecutors' zeal in bringing such charges (Boone and McMichael, 2021). Moreover, although the courts have limited criminal convictions, many women face civil actions including temporary or permanent deprivation of parental rights after a positive drug screen (Boone and McMichael, 2021).

In addition, there is also existing state legislation that has a bearing on research requirements that has nothing to do with abortion politics. For example, New Mexico has a law the prohibits clinical research involving pregnant women except to "meet the health needs of the mother or the fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or (2) there is no significant risk to the fetus."[26] Researchers and their institutions must become and stay familiar with any applicable state law to protect their research and participants. (Sugarman, 2023). The table in Appendix C provides a "snapshot" of some of the state statutes that may affect research studies enrolling pregnant and lactating women.[27] Unfortunately, it is impossible to provide a comprehensive table of all of the laws that might be relevant for conducting research in these populations. Moreover, new statutes and new cases interpreting the listed statutes can be expected over time, so this table is only meant to represent some relevant statues as of January 2024.

Noncompliance with federal regulations can put a sponsor, institution, IRB, or clinical researcher in jeopardy of reputational harm, losing IRB approval of research projects, or in more extreme situations, exclusion from federally funded activities. Failure to adhere to federal and state human subjects research regulations does not in itself create a liability claim for someone who believes that they have been injured by clinical research, but that failure may be important evidence in a negligence claim brought under state law. At the same time, while compliance with federal regulations or guidance is generally not an absolute defense to liability, it can bolster the defense to be able to demonstrate compliance with detailed federal requirements or recommendations for how to study or label a drug.

[26] *Maternal, fetal and infant experimentation*, N.M. Stat. Ann. § 24-9A-3 (May 6, 2021).

[27] Appendix C can be viewed online at https://nap.nationalacademies.org/catalog/27595.

Aspects Specific to Pregnant Women

While the legal bases for liability relating to research with pregnant and lactating women are no different than those that might arise from claims from the general population, there are specific situational aspects and differences in requirements that may affect the nature of that liability, especially for pregnant women.

Informed Consent

Both HHS and FDA have specific rules for informed consent that apply to pregnant women. Subpart B distinguishes between (1) research for the benefit of the pregnant woman or of mutual benefit for the woman and fetus, and (2) research that is done solely for the benefit of the fetus. Regarding research for the sole benefit of the pregnant woman or for the benefit of both the pregnant woman and the fetus, researchers must obtain the informed consent of the pregnant woman. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of both the pregnant woman and the father must be obtained. There are exceptions to the father's consent for unavailability, incompetence, or if the pregnancy is the result of rape or incest.[28] However, Subpart B does not provide a definition for *father*, so it is unclear if that person is the provider of the sperm, which could be a known or anonymous donor, or if that person is the intended coparent, regardless of sex or gender. In addition, HHS regulations provide that if a baby is born, that baby becomes a separate study subject, for whom consent must be given, and special rules apply to research involving neonates.[29]

FDA's draft guidance provides additional guidance for informed consent in studies that involve or may involve pregnant women (FDA, 2018). If the trial is supported or conducted by HHS, then the research must also comply with Subpart B. Informed consent principles dictate that, for a woman who is or may become pregnant, the informed consent process must include any potential risks and the chance of unknown risks to the embryo or fetus, should the woman become pregnant. This information should be included in the informed consent document and the investigator's brochure.[30] Consenting individuals are to be informed of the reasonably foreseeable effect on the fetus or neonate. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their significance in humans. Or, if no such studies have been completed, other pertinent information such as a general assessment

[28] *Research involving pregnant women or fetuses,* 45 C.F.R. 46.204 (e).
[29] *Research involving neonates,* 45 C.F.R. 46.206.
[30] *58 Fed Reg. 39411. (g)* (Jul. 22, 1993).

of fetal toxicity in drugs with related structures or pharmacologic effects should be provided. If no relevant information is available, it is important for the informed consent to explicitly note the potential for fetal risk.[31]

If a participant gets pregnant during a trial, then unblinding would need to occur to determine exposure, and the risks and benefits would need to be reviewed with the participant to determine whether to continue treatment with the investigational drug. A second informed consent process appropriate for pregnant women would then need to take place. Whether or not the pregnant woman continues on the investigational product, it is best practice to collect data from the exposure to the investigational product (FDA, 2018).

Federal regulations maintain the pregnant woman's autonomy to make decisions for themselves and for their fetus. However, when the research is for the benefit of the fetus alone, regardless of whether the research presents less than minimal risk, the consent of the father is also to be obtained.[32] It is not clear how state rules of fetal personhood might affect this framework (Appendix C).[33] To date, there is no indication that state laws on fetal personhood anticipate this question, but some may be interpreted to treat the fetus as legally similar to a child. It is therefore possible that a state may maintain that both parents should legally consent to any research that may affect a fetus (Appendix E).[34] There is an argument that federal human subjects regulations preempt state laws in the context of clinical research, but that is an issue that has not yet been litigated in the courts.

Finally, there may be concerns in some states with restrictive abortion laws. In some states, it may be inappropriate to do some types of research involving pregnant women because the potential legal risks for pregnant women (and potentially their health care providers) are too high (see Appendix E for a full analysis).[35] For example, medication abortion drugs could not be studied. Any drug known to increase pregnancy loss might carry attendant legal risks that are too high. Even in studies that can go forward, the informed consent may need to include risks associated with potential pregnancy loss, availability of abortion or contraception, possible effects on the fetus, and the risks of pregnancy information and outcomes being recorded, reported, or assessed by state officials. The use of certificates of confidentiality may obviate some of these privacy risks, but it may not be possible to eliminate all of these risks. The frequent,

[31] *58 Fed Reg. 39411. (g)* (Jul. 22, 1993).
[32] *Research involving pregnant women or fetuses,* 45 C.F.R. 46.204 (e).
[33] Appendix C can be viewed online at https://nap.nationalacademies.org/catalog/27595.
[34] Appendix E can be viewed online at https://nap.nationalacademies.org/catalog/27595.
[35] Appendix E can be viewed online at https://nap.nationalacademies.org/catalog/27595.

often back-and-forth changes being seen in abortion laws, particularly as some laws are being challenged in courts, means that sponsors may want to engage experienced legal counsel to ensure their trials remain compliant with changing state laws, which remain in a constant state of flux (Sugarman, 2023). Restrictive abortion laws should not affect clinical trials with lactating women, unless the lactating woman is also pregnant.

Long-Tail Effects

One important aspect that may affect liability related to pregnant women is the potential for long-tail claims. A long-tail claim "involves tortious or other liability-creating conduct that causes latent bodily injury or property damage that then manifests itself only many years, and sometimes decades, after the harm-causing conduct occurred" (Abraham, 2021). Another characteristic of long-tail claims is that because the damage or harm is hidden for years, they may involve hundreds or even thousands of claimants. One of the best-known examples of long-tail liability in tort involved DES, which was prescribed to pregnant women to prevent miscarriages but was later linked to cancers for them and their daughters, infertility, reproductive anomalies, and poor pregnancy outcomes in their female children and urogenital and sperm abnormalities in their male children (see Box 2-1). It has been estimated that up to 10 million people (pregnant women and their offspring) were exposed to DES (Hammes and Laitman, 2003). Long-tail claims are not unique to the context of pregnant women or even to medical product litigation, although the first recognized long-tail case involved an anticholesterol drug that caused cataracts.[36] Because certain harms can take years to manifest in a child exposed in utero to particular medical products—and the statute of limitations does not start to run until the child reaches the age of majority (i.e., age 18, in most states)—this creates a longer window of time for plaintiffs to file suit. In addition, long-tail effects may mean that the conduct gives rise to at least two categories of potential future litigants: the pregnant woman and their offspring (Mastroianni et al., 2017).

It must be emphasized that long-tail liability concerns, while real, do not make such cases any more likely to prevail. These cases are subject to the same requirements described above, and the obstacles to meeting those requirements, starting with proof of causation, remain high. Moreover, long-tail liability is not a reason to avoid clinical research with a medical product that is expected to be used broadly by pregnant women. Clinical trials are the gold standard for accurately determining causation versus association and likely the best way to develop an accurate signal

[36] *Roginsky v. Richardson-Merrell, Inc.,* 378 F.2d 832, 834 (2d Cir. 1967).

of more common adverse events and may help avoid additional liability later. Nonetheless, long-tail liability concerns are likely to affect medical product development and marketing risk–benefit calculations for sponsors, particularly with respect to rarer adverse events that are unlikely to be identified during preapproval clinical studies. Cases that potentially involve hundreds of claimants may pose litigation risks that sponsors are unwilling to undertake. Even in cases where the defendant may be relatively certain that their product did not in fact injure the claimants, the certainty provided by settlement, even for very large amounts, may be preferable to the risk posed by a legal trial (Abraham, 2021).

Parental Liability

The case law analysis provided in Appendix B does not reveal any legal liability exposure related to parents' participation in clinical research. Many states have some level of parent–child immunity that would preclude such litigation. There are a few atypical cases, however, that have recognized a potential claim by a child against a mother whose negligence caused damages in utero (Clayton, 1994), one of which is a case against a mother who took medication while pregnant that claims she failed to exercise "reasonable parental discretion."[37] Participation in clinical research might insulate against such claims since the independent review may serve as additional evidence of "reasonableness," unless, of course, the research itself were subject to inquiry. In addition, in the general context of whether a mother can be held liable to her child for negligence while pregnant, courts tend not to recognize such a claim although they would likely recognize a claim against a third-party.[38] As noted by the Massachusetts Supreme Court, "recognizing a pregnant woman's legal duty of care to her unborn child would present an unlimited number of circumstances that would likely give rise to litigation."[39] This is also addressed in the Third Restatement of Torts, which reads "A number of courts have decided that mothers owe no duty of care to their unborn fetuses because of the infringement on autonomy and personal choice that such a duty would impose" (American Law Institute, 2010).

Following the U.S. Supreme Court decision in *Dobbs v. Jackson Women's Health Organization*, overturning its previous rulings that the U.S. Constitution protected the right to an abortion, research participants may

[37] *Grodin v. Grodin,* 301 N.W.2d 869 (Mich. App. 1981).

[38] See, e.g. *Remy v. MacDonald*, 801 N.E.2d 260, 263 (Mass. 2004); *Stallman v. Youngquist*, 531 N.E.2d 355, 359 (Ill. 1988); *Chenault v. Huie*, 989 S.W.2d 474, 477 (Tex. App. 1999) (specifically rejecting *Grodin v. Grodin*).

[39] *Remy v. MacDonald*, at 263.

be exposed to new legal liability risks depending on state laws and local enforcement (Appendix E).[40] The *Dobbs* decision has also contributed to creating a climate of uncertainty owing to a changing legal landscape in some states. A number of states have broad child abuse statutes that might be interpreted to expose a mother to liability because of medications taken while pregnant. Privacy concerns have long been a necessary consideration for research involving pregnant women, and there is evidence that some states could attempt to expand their reporting requirements to clinical trial sponsors if they become aware of an induced or spontaneous abortion that might take place during clinical research.

Liability for Vaccines

The liability landscape for vaccines differs from that of most other medical products because of the availability of a federal no-fault compensation scheme for certain on-market vaccines. Notably, however, with one narrow exception applicable to vaccines in public health emergencies, there is no such scheme applicable to research-related vaccine injuries.

The Vaccine Injury Compensation Program (VICP) addresses injuries stemming from covered vaccines. As a result, manufacturers of those vaccines and providers who administer them are largely shielded from vaccine-related liability (Jacobs, 2012). The VICP, which is funded by a small excise tax on covered vaccines, provides compensation for vaccine injuries related to vaccines recommended by the Centers for Disease Control and Prevention (CDC) for routine administration to children and/or pregnant women.[41] The Cures Act amended the Vaccine Act to permit VICP claims filed on behalf of live-born children for injuries allegedly sustained in utero that are attributable to maternal vaccination.[42] Notably, not all vaccines are part of the VICP. For example, the shingles vaccine, which is designed only for adult populations, is not covered by the VICP.

The VICP was created in the 1980s after litigation against both vaccine companies and health care providers threatened to create vaccine shortages and reduce vaccination rates (HRSA, 2023). Compared to drugs designed to treat medical conditions, vaccines are known to carry a higher risk of liability because they are distributed widely to the general, healthy public; therefore, there are disincentives for pharmaceutical companies

[40] Appendix E can be viewed online at https://nap.nationalacademies.org/catalog/27595.

[41] *National Vaccine Injury Compensation Program,* CDC; 42 U.S.C. §§ 300aa-10 et seq. (Dec. 19, 1989).

[42] *Petitions for compensation,* 42 U.S.C. 300aa–11(f). (2016).

to engage in the research and development of vaccines. The availability of the VICP encourages companies to pursue vaccine research and development by counterbalancing concerns about the unpredictability of the law, potential for large damages awards, and negative press attention (Winter et al., 2021). The VICP only applies to marketed vaccines; it does not protect companies during vaccine development.

Although injured persons can reject a no-fault award and sue the vaccine manufacturer, the statute creates disincentives for doing so, and lawsuits involving covered vaccines are relatively rare. In addition, in 2011, the Supreme Court ruled that design-defect claims are preempted by federal law.[43] While the VICP has been very successful in mitigating liability for vaccine manufacturers and promoting vaccine production, there is evidence that it is suffering strains owing to significant growth in complaints and inadequate staffing, leading to long wait times for petitioners (Gentry and Hughes, 2023).

Another liability protection program for vaccine manufacturers was created in the PREP Act, enacted in 2005 as an amendment to the Public Service Act. The PREP Act allows the secretary of HHS to issue a declaration providing immunity from tort liability for vaccines and other countermeasures developed to combat a public health emergency. In addition, the PREP Act authorizes compensation by the Countermeasures Injury Compensation Program (CICP) for individuals who are seriously injured by covered countermeasures such as vaccines. Unlike the VICP, the CICP can apply to products in development and those that have received an emergency use authorization from FDA.

The PREP Act was invoked in March 2020 to provide liability protection to parties developing countermeasures against COVID-19. Despite the broad no-fault compensation scheme, pregnant and lactating women were excluded from the COVID-19 vaccine trials that preceded FDA's authorization of the vaccines for use in the adult population. However, according to records from ClinicalTrials.gov, only two clinical studies with pregnant women were conducted. These were started after the initial authorizations, and there have been no resulting publications catalogued in the study record (ClinicalTrials.gov, 2023a,b). No clinical studies on the COVID-19 vaccines for lactating women were reported in ClinicalTrials.gov. Postmarketing studies and surveillance of the vaccine in pregnant and lactating women eventually demonstrated its safety and effectiveness for these populations long after the vaccine was available (Muyldermans et al., 2022; Prasad et al., 2022). This led to confusion and hesitancy to receive the vaccine among pregnant and lactating women (Bianchi et al., 2022), which particularly for pregnant women, who are at higher risk

[43] *Bruesewitz v. Wyeth LLC.*, 562 U.S. 223 (2011).

of severe symptoms and death from COVID infection, is likely to have resulted in poorer health outcomes for the pregnant women and their offspring (Rubin, 2021).

CONCLUSIONS

Conclusion 2-1: 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.

Conclusion 2-2: 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 2-3: Perceptions of liability for including pregnant women in clinical research exceed any actual liability. Perceptions of liability are based on cultural narratives, which conflate clinical research with pregnant women with historical examples of drugs that were not subject to modern drug evaluation processes; ignore the potential benefits to pregnant and lactating women, their fetuses, and children resulting from research; and fail to account for the risk of harm and ensuing potential for liability resulting from failure to conduct clinical research in pregnant and lactating persons.

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3

Strategies to Reduce Harm Through Clinical Research

The most straightforward way to mitigate liability is to prevent harm in the first place. While it is impossible to eliminate *any* possibility of injury during clinical research, and therefore impossible to completely avoid any liability risk, it *is* possible to limit the likelihood of injury. The regulatory system and required ethics oversight, review, and approval of medical products are designed to protect the rights and welfare of human participants in clinical research and ensure that medical products are generally safe and effective before they go onto the market for general use. A key component of that review and evaluation is ensuring that risk of harm—which encompasses the probability and magnitude of harm—to research participants is minimized to the extent possible. Not only does the regulatory system and ethics oversight aim to reduce the risk of harm to research participants, but it also ensures that the risk of harm is reasonable in relation to the anticipated benefits of participating in clinical research.

In clinical research involving pregnant and lactating women, reducing harm to the fetus and child is of paramount concern to research participants, sponsors, investigators, and institutional review boards (IRBs) (Wada et al., 2018; Wang et al., 2017; Zhao et al., 2018). However, it should be noted that the risk of harm in lactation studies is different than in pregnancy studies. Risk of harm during lactation is much lower to the offspring, as the majority of medications on the market (about 90 percent) are considered safe for breastfeeding because the drug concentration in the milk is low enough to be considered safe for breastfeeding children

(Newton and Hale, 2015). As discussed in Chapter 2, liability for pregnant women and lactating women often is conflated. This applies to risk of harm as well, resulting in a dearth of information on dosing, safety, and efficacy of medical products in lactating women.

As summarized in Chapter 1, the desire to avoid harm to pregnant and lactating research participants, as well as their fetuses and children, is a central factor that has resulted in decisions to exclude them from participating in clinical research entirely. However, their exclusion from clinical research can result in harm in the clinical practice setting from inadequate or inappropriate treatment in the absence of evidence from clinical studies. There are two types of potential harm that require mitigation strategies: harm from exclusion from research—which can manifest in multiple ways including lack of treatment options, lack of evidence to make informed decisions, and outdated treatment regimens—and harm from participation in research, which can involve harm to research participants and their fetus or child and harm to the general populations when access to medical products are delayed. This chapter seeks to reduce both types of harms through the conduct of research involving pregnant and lactating women in a way that reduces harm to the participant and their fetus or child.

This chapter is divided into four sections. An introduction to the medical product development pathway is followed by discussions of strategies to reduce harm through the application of Food and Drug Administration (FDA) guidance and regulations, the application of U.S. Department of Health and Human Services (HHS) and FDA protections for human subjects, and through research design. The first section, a review of the medical product development pathway, is meant to provide a necessary and important background for the current system of development, including the studies required to move along this pathway. The second section, reducing harm through FDA guidance and regulations, provides an overview of the current rules and guidance documents applicable to conducting research with pregnant and lactating women and offers suggestions for potential improvements to current FDA guidance and regulations. The third section, reducing harm through HHS and FDA protections for human subjects, describes federal regulations that guide the ethical conduct of human subjects research to protect research participants from potential harms. And lastly, the fourth section examines reducing harm through research design and how different study designs and methodologies could be employed to improve data collection and reduce harm to research participants. Importantly, this chapter provides evidence that although the current drug development pathway and regulations go a long way towards reducing harm, there are opportunities to make them better for pregnant and lactating women.

INTRODUCTION TO THE MEDICAL PRODUCT DEVELOPMENT PATHWAY

As discussed in Chapter 2, thalidomide has shaped the United States' approach to inclusion of pregnant women in clinical research in meaningful ways. In 1962, in response to the effects of thalidomide, Congress passed the Kefauver-Harris Drug Efficacy Amendments to the Food Drug and Cosmetic (FD&C) Act, which strengthened the licensure system for new drugs, giving FDA authority to refuse approval of any new drug application that did not meet safety, effectiveness, and labeling requirements.

The current medical product development pathway is designed to ensure that risk of harm is minimized for the individuals who participate in clinical research and for the individuals who may use the product once it is on the market (Berlin et al., 2008). Rigorous preclinical and then clinical studies must be conducted prior to product approval to demonstrate that the product has a favorable benefit–risk balance for use in its intended population. Despite these requirements, pregnant and lactating women often must use FDA-approved products on-label without accompanying safety, efficacy, and dosage data tailored to the pregnant and lactating population (Byrne et al., 2020). This section provides a brief overview of the current U.S. medical development pathway, which is a critical precursor to understanding how to improve current systems to safely include pregnant and lactating women in critical research studies.

Preclinical Development Studies

The goal of preclinical development studies is to serve as a bridge between initial laboratory findings that hold promise for a therapeutic target and use of the experimental product in a clinical setting. Preclinical studies include the development of animal models that are predictive of the pharmaceutical agent's activity, toxicokinetic and nonclinical pharmacokinetic studies, identification of biomarkers that quantify the activity of interest and potential safety parameters of the therapy, establishment of a dose–response relationship for the product, construction of an initial dosing schedule for human pharmacokinetics and pharmacodynamics (PK/PD) studies, and optimization of the dosing regimen, including route of administration. This section explores three broad areas of preclinical studies. This section applies to most medical products in development, although FDA does have product-specific guidance for vaccines for infectious diseases and for oncology products.[1]

[1] Appendix C provides a full overview of these product-specific guidances and is available at https://nap.nationalacademies.org/catalog/27595.

Pharmacokinetic and Pharmacodynamic Studies

Preclinical PK/PD studies anticipate the kinetics (how a drug moves throughout the body) and dynamics (biochemical, physiologic, and molecular effects of the product on the body) to be expected when studies are subsequently conducted in humans. These are single-dose and multidose escalation studies that integrate activities collectively known as ADME into the process:

1. **A**bsorption of the experimental product following different routes of administration,
2. **D**istribution of the experimental product to organ systems,
3. **M**etabolic pathways of the experimental agent, and
4. **E**xcretion mechanisms of the experimental product through organ systems.

Genetic Toxicity and Carcinogenicity Studies

Genetic toxicity studies involve examining the potential for gene mutation in bacteria and assessing the potential for chromosomal damage in mammalian cells or in an vitro assay (FDA, 2006). These results inform the determination of whether the product development process may proceed to human studies.

Lifetime carcinogenicity studies in rodents are intended for experimental agents that are expected to be administered to patients on regular schedules for substantial parts of their lives (FDA, 1996). These studies are often conducted in conjunction with genotoxicity studies, toxicokinetic studies, and mechanistic studies to form a more detailed picture of carcinogenic potential. Results of these studies help to contextualize the eventual formation of the benefit–risk picture. Because low percentages of new molecular entities at this stage of development eventually reach the stage of submission of a New Drug Application (NDA), carcinogenicity studies are generally not conducted until much later in the development cycle.

Developmental and Reproductive Toxicology (DART) Studies

DART studies identify the experimental product's adverse effects seen in animal species that may portend the types of toxicities that could occur in humans, including evaluation for teratogenicity. The results of these preclinical studies aid in selecting an initial starting dose and a potential dose titration schedule, and the results aid in estimating the probable highest safe dose for human clinical trials, while also initially characterizing potential adverse effects that might occur in humans (ICH, n.d.). DART studies are categorized into three segments according

TABLE 3-1 Developmental and Reproductive Toxicology (DART) Studies

Category	Name	Administration and Observation Timing	Target for Observation	Typical Species
Segment I	Fertility and Early Embryonic Development (FEED)	From production of gamete to mating for males, and through implantation for females	Estrous cyclicity, spermatogenesis, mating behavior, fertilization, early embryogenesis	Rodent (rat or mouse, both sexes)
Segment II	Embryo-fetal development	From implantation to closure of hard palate	Late embryogenesis, early fetal development including major organ formation	Rodent (female rat or mouse), nonrodent (female rabbit)
Segment III	Pre- and postnatal development	From closure of hard palate to weaning (observation includes second generation)	Late fetal development, parturition, lactation, weaning, offspring growth, maturation including second generation	Rodent (rat or mouse, both sexes)
N/A	Juvenile	From neonate stage to adolescence	Pediatric population	As relevant

SOURCE: Derived from FDA, 2021; with additional information from Premier Consulting, 2021.

to the stage of development during which the experimental product is administered (Table 3-1). A fourth category (Juvenile) provides data on the experimental product's potential effect in the pediatric population.

Clinical Development Studies

Prior to the initiation of a clinical study of a new investigational product in humans, the sponsor must submit an Investigational New Drug Application (IND) to FDA (FDA, 2018e). In the application, the clinical investigator includes PK/PD and toxicology data from the preclinical animal studies, manufacturing information, clinical protocols for intended studies to be conducted in humans, data from any prior human research, and information about the investigator. This section provides a description of the phases of drug development and in following sections specifies the FDA guidance and special considerations for research with pregnant and lactating populations.

Phase I Studies

Once the sponsor completes preclinical studies that demonstrate the product is anticipated to be generally safe when used in humans, development can proceed to Phase I studies in human volunteers. The standard approach to Phase I studies begins with a single-dose escalation study (Figure 3-1). Usually, these studies begin by dosing three to five volunteers, at a dose anticipated to have no observable effect, determined during preclinical studies. The amount of the single dose is gradually increased over days or weeks, noting gradual changes in symptoms, physical exams, and laboratory values. This dose escalation schedule continues until a critical value of tolerance is reached, identified as the dose-limiting toxicity. Thereafter, the next lower dose level is identified as the maximum tolerated dose.

The range of the dose amounts between those associated with the first onset of observable effects and the maximum tolerated dose is known as

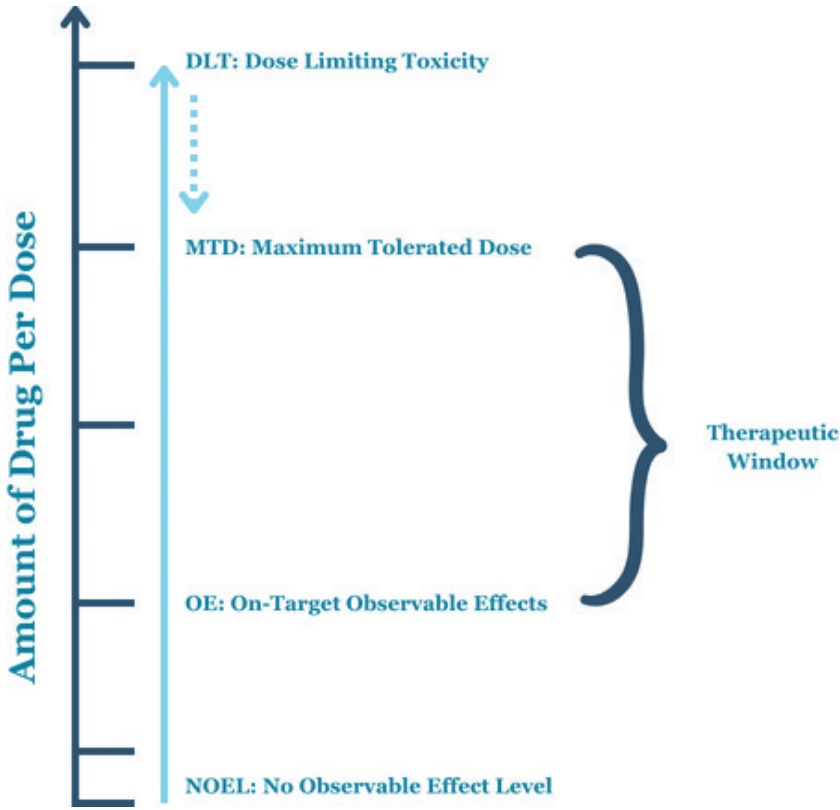

FIGURE 3-1 Phase 1: Dose escalation.
SOURCE: Beninger, 2024.

the therapeutic window, which serves as the range of doses to be evaluated during Phase II studies. Analysis of the PK/PD assists in narrowing the dose range of interest, setting the dosing interval, helping to estimate the duration of dosing for later studies when appropriate, and proposing the features of the safety profile. Multidose studies generally follow with a separate cohort of volunteers, based on the now available human PK parameters.

Phase II and Phase III Studies

Phase II studies generally begin in volunteers either with, or at risk for, the disease of interest. The goal is dose selection, the process is dose finding, and the numbers generally range from 100 to 300 volunteers (Table 3-2). Depending on whether treatment is anticipated to be time limited (e.g., for treatments in oncology and infectious diseases) or indefinite (e.g., for cardiovascular diseases and diabetes mellitus), the dosing schedule of amount and duration considers the effects on the markers of

TABLE 3-2 Common Parameters of Studies Conducted During Clinical Development

	Phase I	Phase II	Phase III	Phase IV
Relevant regulations	21 CFR 312.21(a)	21 CFR 312.21(b)	21 CFR 312.21(c)	21 CFR 312.85
Research participant characteristics	Healthy volunteers	Volunteers with condition being studied	Volunteers with condition being studied	Individuals using product post-approval, may or may not be enrolled in study
Size of study population	<100	100–300	>1000	Potentially anyone using the product (>1000)
Evaluated outcomes	Safety	Safety and efficacy	Safety and efficacy	Safety, efficacy in new populations and new indications, pharmacoeconomics, quality of life
Study design	PK/PD study	Usually randomized, placebo-controlled trial	Randomized, blinded, placebo-controlled trial	May be interventional or observational

NOTES: This applies to clinical trials broadly, but there are notable exceptions, particularly for healthy volunteer participation in Phase I trials in some trials such as oncology or HIV trials. The number of participants in each phase is largely determined by the condition being studied and the size of the patient population. PK = pharmacokinetics; PD = pharmacodynamics.

benefit and the accompanying safety profile. The Phase II studies may include two or more dose amounts and are often conducted with control arms for placebos or active comparators.[2]

Phase III studies are conducted in thousands of patients with the doses (amount and schedule) expected to be marketed, guided by the results of the Phase II studies. These studies are conducted to collect the quantitative statistical data that will support the commercial sponsor's New Drug Application (NDA). Phase III is also commonly a time to conduct the increasingly important pharmacogenomic studies (FDA, 2021), as well as expected drug–drug interaction studies.

Product Review and Approval

Once the phased studies are complete, the commercial sponsor then submits an NDA or a Biologics License Application (BLA) to FDA, the approval of which is required before marketing the product is permitted. FDA is the regulatory agency with the statutory authority and the responsibility for determining whether an NDA or BLA provides substantial evidence to support the safety and effectiveness of the therapeutic product under consideration. FDA approval means that the data on the use of the therapeutic product is determined to provide benefits that outweigh its known and potential risks for the intended population (FDA, 2018b, 2022).

Prescription labeling represents what FDA determines to be the relevant experimental evidence that supports the safety and effectiveness of the use of the agent in patients with diseases, conditions, or circumstances indicated for prophylactic use, organized and presented in a standardized format. Labeling for prescription medicines is required for all FDA-approved prescription drugs and biological products and contains a summary of the essential scientific information needed for the safe and effective use of the medicine.[3]

When a prescription product is approved for use in adults, the product is also approved for use in pregnant and lactating women by default unless there is a clear contraindication or warnings against the product's use during pregnancy or lactation, which must then be included on the product label. This is because pregnant and lactating women are considered a subpopulation of the adult population and, therefore, absent a contraindication or warnings against the product's use during pregnancy or lactation, they are not excluded from the approved population when a drug or biological product is approved for use in adults.

[2] Phases of an Investigation, 21 CFR 312.21.
[3] *New Drugs,* 21 USC § 355, (Jan. 7, 2011).

REDUCING HARM THROUGH FDA REGULATIONS AND GUIDANCE

FDA has developed several guidance documents relevant to clinical research that includes pregnant or lactating women. "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials" provides considerations for when to include pregnant women in clinical research (FDA, 2018d). "Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling" details the agency's recommendations for designing and conducting PK studies in pregnant women (FDA, 2004). "Postapproval Pregnancy Safety Studies" provides guidance on conducting observational studies in pregnant women after a product has received approval from FDA (FDA, 2019b). And "Clinical Lactation Studies: Considerations for Study Design," offers guidance on conducting studies that evaluate the safety and efficacy of drugs in lactating women (FDA, 2019a). As mentioned in Chapter 2, rules and regulations are legally enforceable, whereas guidance documents are not. However, there is generally little practical difference in how industry sponsors adhere to the two types of regulatory information (Seiguer and Smith, 2005). This section discusses different types of FDA regulatory information relevant to pregnant, potentially pregnant, and lactating women and offers suggestions for how this guidance might be improved to reduce harm for pregnant and lactating women, and their fetuses and children.

FDA Guidance on Preclinical Studies for Pregnant Women and Potentially Pregnant Women

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) strives to have better regulatory harmonization worldwide to ensure safe and effective development of medications. FDA is a founding member of ICH and plays a major role in the development of ICH guidelines, which FDA then adopts and issues as guidance to industry.

As mentioned above, genetic toxicity studies are critical for examining the potential for a product to cause gene changes in mammalian cells. According to ICH guidelines, all preclinical female reproduction toxicity studies and standard genotoxicity tests should be completed before the inclusion of potentially pregnant women not using highly effective birth control in any clinical trial (ICH, n.d.).

Highly relevant to the participation of women who are pregnant and potentially pregnant are the completion of DART studies. ICH recommends conducting DART studies to characterize the risk of the experimental product and take appropriate precautions during exposure of potentially pregnant women in clinical trials, or to limit the risk by taking

precautions to prevent pregnancy during clinical trials (ICH, n.d.). In the United States, embryo-fetal development studies (Segment II) for most products can be deferred until the initiation of Phase III trials, the final phase of clinical research prior to submitting marketing applications if precautions are taken to prevent pregnancy in potentially pregnant women (exceptions exist for oncology products to treat advanced cancer). FDA does not require that pre- and postnatal development studies (Segment III) be submitted until the sponsor seeks approval of the product.

If DART studies were conducted earlier in the product development pathway, it could provide an opportunity to begin clinical phases of research with pregnant women sooner (Sewell et al., 2022). Earlier DART studies could shorten the time that pregnant patients and their health care providers must wait for high-quality evidence generated in later stages of clinical research. Further, earlier completion of DART studies would allow for earlier detection of potential harmful pharmaceutical and biopharmaceutical products for pregnant and lactating women and their offspring. Timely conduct of DART studies could also enable women who become pregnant over the course of a clinical trial to remain in the trial once pregnant, which would provide critical information about the use of the product in early pregnancy.

A critique of conducting DART studies earlier in the clinical development process is that doing so before having defined the dose in the general human population could increase the cost of research and delay timelines for approval of the product (Sewell et al., 2022). Although this is a valid concern, waiting to conduct relevant DART studies can delay later stages of research by requiring sponsors to update protocols according to DART study results. Additionally, DART studies can feasibly be conducted without delaying product approval by beginning to conduct DART studies as soon as the dose to be used in Phase III studies for the general population is determined.

Preclinical studies, in general, may not be highly predictive of human responses. For a study of 108 oncology drugs, animal toxicity did not show a strong predictive correlation with human toxicity; the median positive predictive value was 0.65 and the negative predictive value was 0.50 (Atkins et al., 2020). It is not known how well DART studies predict potential outcomes in humans, nor are DART studies routinely designed to capture specific outcomes that may be relevant to later studies in humans. For example, in utero fetal exposure to products may affect immune system development, higher-order learning and memory, and endocrine functioning, but fetal exposure concentrations of drugs are not typically assessed in DART studies (Sewell et al., 2022); yet, such data are critically important to further demonstrate the safety of a product in pregnant women and can only be captured in specially designed studies. Thus, investigators must be attentive to, and discerning with, the results from DART studies.

One potential way to exercise greater care in the conduct of these studies is with the selective use of data safety monitoring boards (DSMBs) during the conduct of Phase I studies (see Box 3-1). While few adverse events may be detected during Phase I studies owing to the small number of enrolled participants, use of a DSMB could rapidly evaluate adverse events that do arise during this early stage of clinical development and halt exposure of the product to additional participants if necessary.

BOX 3-1
Data Safety Monitoring Boards

DSMBs, also known as data monitoring committees, are a group of independent experts without a vested interest in the clinical trial and who review evidence of adverse events and the outcomes of the trial to recommend whether a trial should be continued, altered, or terminated. DSMBs are generally unblinded to trial safety data, allowing them to make decisions about the scientific integrity of the clinical trial so sponsors and study investigators can remain blinded to trial results (Evans, 2022).

All trials require safety monitoring, but not necessarily from an independent body like a DSMB. A DSMB can be requested by the IRB overseeing the trial protocol. In addition, the National Institutes of Health (NIH) requires that each institute and center within NIH have its own system and requirements for data safety and monitoring. The NIH policy does not require DSMBs for all clinical trials, but states that "monitoring should be commensurate with risks—The method and degree of monitoring needed is related to the degree of risk involved" (NIH, 1998). Industry sponsors do not have specific requirements related to DSMBs, but in 2024, FDA issued draft guidance on DSMBs for use by clinical trial sponsors. FDA's "Use of Data Safety Monitoring Committees in Clinical Trials: Guidance for Industry" suggests the value of using DSMBs, including when:

- there is "limited experience in a therapeutic area or participation of subjects from a vulnerable population";
- research subjects are "at risk of serious morbidity or mortality" or if the adverse advent may be anticipated in the population enrolled in the study regardless of the investigational product;
- there is sufficient time for a DSMB to have a meaningful impact on the trial, including sufficient time for safety oversight and DSMB evaluation (FDA, 2024b).

DSMBs may be particularly useful in research that includes pregnant women, because independent data reviewers are empowered to identify and remedy any safety concerns that arise while the research is being conducted (Evans, 2022). For example, Pfizer used a DSMB for its trials testing a maternal respiratory syncytial virus vaccine that received FDA approval in 2023 (NASEM, 2023; FDA, 2023b). Should a serious safety signal be detected during the research, a DSMB could intervene to mitigate or prevent additional harm.

FDA Guidance on the Inclusion of Pregnant and Potentially Pregnant Women in Clinical Studies

For sponsors who plan to include pregnant women in clinical trials of their investigational drug, biological product, or medical device, FDA recommends that sponsors be prepared to discuss such plans with the appropriate FDA review division early in the development phase, and such discussions should involve FDA experts in bioethics and maternal health (FDA, 2018c). However, these discussions are sponsor initiated and not required when pregnant women are not included in the clinical trial.

At the time of IND application submission for products to treat conditions that are not specific to pregnancy, there is rarely any information or consideration of the dosing, efficacy, or safety of the investigational therapeutic agent in pregnant women at this stage. However, according to FDA's draft guidance for drug developers, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," pre-IND and later clinical-stage meetings between FDA and sponsors may include discussion of trial populations as well as design plans (FDA, 2023d). Therefore, these meetings could provide opportunities for sponsors to discuss plans for involving pregnant and lactating women in their clinical development programs.

FDA's draft guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials," published in 2018, provides the most expansive current guidance to industry on how and when to include pregnant women in clinical trials for drugs and biological products. This guidance discusses both the scientific and ethical issues that sponsors should address when considering the inclusion of pregnant women in clinical trials.

This 2018 draft guidance states that pregnant women may be enrolled in clinical trials that involve greater than minimal risk to the fetuses. When a trial offers the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses, it can be acceptable to expose a fetus to greater than minimal risk. FDA provides examples of when such exposure would be acceptable, which include when a trial offers a needed but otherwise unavailable therapy or when a drug or biological product being studied reduces the risk of acquiring a serious health condition (FDA, 2018c). However, the guidance does not define "greater than minimal risk" clearly or provide many examples, which can cause confusion in interpreting the guidance for sponsors and IRBs.

The 2018 draft guidance also includes information on the timing of enrollment for involving pregnant women in clinical trials. According to the draft guidance, Phase I and Phase II clinical trials in nonpregnant women, including potentially pregnant women, should be completed before enrolling pregnant women into later phases. The guidance also lists situations that might affect the decision of when to enroll pregnant

women in a trial, including if there are other approved treatments available, if there are limited therapeutic options, or if safety data are available for a drug that has been studied for other indications or for use in other populations (FDA, 2018c).

However, current guidance does not set clear expectations for when pregnant women should ideally be included in clinical studies, other than what studies must be completed in nonpregnant women first. The lack of clear expectations results in most sponsors' never conducting studies with pregnant women. Further, FDA does not provide guidance on conducting clinical studies for conditions specific to pregnancy, particularly when the study is for a new product without human safety data. These studies pose a different set of considerations from products to treat general conditions and warrant a specific discussion in guidance documents, especially for study design.

FDA Guidance on Conducting Clinical Studies with Pregnant Women

PK/PD Studies

FDA's 2004 final guidance, "Pharmacokinetics in Pregnancy, Study Design, Data Analysis, and Impact on Dosing and Labeling," provides specific recommendations for designing and conducting PK/PD studies in pregnant women and lays out a framework to stimulate further study and research to assist in rational therapeutics for pregnant patients. FDA acknowledges that (1) pregnant women are "actively excluded" from clinical trials, (2) data in product labels regarding PK and dose adjustments during pregnancy rarely provide information for appropriate prescribing in pregnancy, and (3) there has been a significant amount of pharmacological research conducted to improve the quality and quantity of data available for other altered physiologic states (e.g., patients with renal and hepatic disease) and subpopulations (e.g., pediatric patients). Because of that, FDA has stated that "The need for PK/PD studies in pregnancy is no less than for these populations, nor is the need for the development of therapeutic treatments for pregnant women" (FDA, 2004).

This guidance specifies that pregnant women may be involved in PK studies if the following conditions are met:[4]

- Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses (FDA, 2004).

[4] *Research Involving Pregnant Women or Fetuses,* 45 CFR Subpart B, § 46.204 (Nov. 3, 2001).

- The risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means (FDA, 2004).

The guidance also recommends that PK studies be conducted if the following occurs:

1. the drug is known to be prescribed in or used by pregnant women, especially in the second and third trimesters;
2. for a new drug or indication if there is anticipated or actual use of the drug in pregnancy;
3. use is expected to be rare but the consequences of the uninformed dosages are great (e.g., for drugs with narrow therapeutic ranges and for cancer chemotherapeutic agents), and
4. if pregnancy is likely to alter significantly the PK of a drug (e.g., for drugs that are renally excreted) (FDA, 2004).

FDA further states in this guidance:

> Although PK studies in pregnancy can be considered in Phase III development programs depending on anticipated use in pregnancy and the results of reproductive toxicity studies, FDA anticipates that most PK studies in pregnant women will occur in the postmarketing period and will be conducted using pregnant women who have already been prescribed the drug as therapy by their own physician (FDA, 2004).

Given the known physiological changes that occur during pregnancy, it is critical that clinical studies investigate PK/PD during all phases of pregnancy. Despite this, PK/PD studies are often not available for common medications used during pregnancy and rarely are PK/PD studies conducted in all phases of pregnancy (Coppola et al., 2022). It is critical that more PK/PD studies are conducted throughout pregnancy and the postpartum period to better understand appropriate dosing. Therefore, although current FDA guidance recommends PK studies be conducted if the product is going to be used by pregnant women, more concrete time lines for conducting PK/PD studies and additional guidelines on completing studies throughout stages of pregnancy may encourage sponsors to complete more of these studies.

Data Collection

When pregnant women are enrolled in a clinical trial, FDA's draft guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials," provides that data collection elements should

include (at a minimum): (1) gestational age at enrollment; (2) gestational timing and duration of drug exposure; and (3) pregnancy outcomes including adverse maternal, fetal, and neonatal events. Further, the draft guidance states while all clinical trials require monitoring, clinical trials that involve pregnant women should include a data monitoring plan that includes members with relevant specialty and perinatal expertise to permit ongoing recognition and evaluation of safety concerns that arise during the course of the trial (FDA, 2018c). However, the guidance provides few details on the content or format of such a plan, including few details on the duration of infant follow-up or infant outcomes or acceptable research designs to collect such information. More detailed guidance on the proper monitoring and follow-up that industry could conduct for research involving pregnant women would help minimize harm for these populations.

Finally, while PK studies can provide information on appropriate dosing and basic safety, they are not capable of determining the efficacy of a medical product or describing the safety of long-term exposure that might be expected from routine clinical use. While it is understandable that FDA would not want to be overly prescriptive in how to evaluate the safety and efficacy of a product in pregnant women given the potential diversity of products and therapeutic targets, additional information that is currently *not* discussed in FDA guidance to establish a product's safety profile and efficacy in pregnant women could be helpful for sponsors. For example, information on what data FDA considers sufficient evidence to describe safety in pregnant participants would facilitate this research and could help sponsors develop labeling that is more useful for pregnant patients and their providers.

FDA Guidance Addressing Lactating Women in Clinical Research

Drug exposure and risks during the lactation period are generally lower than pregnancy and depend on whether the child is breastfeeding, the transfer of the drug into human milk, and the absorption, metabolism, and elimination of the drug by the breastfed child (Newton and Hale, 2015). In 2019, FDA updated its draft guidance, "Clinical Lactation Studies: Considerations for Study Design," which provides recommendations for sponsors conducting pre- or postmarketing clinical lactation studies. The guidance clarifies that although FDA has required lactation studies under Section 505(o)(3) of the FD&C Act under certain circumstances to inform breastfeeding with drug use recommendations included in the "Lactation" subsection of labeling, the guidance states that FDA "is considering additional circumstances in which lactation studies may be required" (FDA, 2019a).

According to FDA guidance, lactating women may participate in clinical lactation studies if they are prescribed a medically necessary drug in the postapproval setting as part of standard clinical care and are allowed to continue breastfeeding while taking the drug. For new investigational drugs, lactating women who are administered an investigational drug for a disorder or condition must discontinue breastfeeding because of the potential or unknown risk to the infant and milk must be discarded for a duration depending on the half-life of the medication. For healthy volunteers who participate in a trial of an investigational drug for research, breastfeeding must be discontinued for the duration of the study.

There are three main types of study designs for clinical lactation studies:

1. Lactating women (milk only) study: Human milk is collected, and drug concentrations determined. These may be used to estimate drug transfer to the milk to determine whether there are clinically relevant concentrations in human milk, and to evaluate effects of the drug on milk production. Most published studies are in this category.
2. Lactating women (milk and plasma) study: Milk and plasma are collected from lactating women, and pharmacokinetic data is gathered as well as data regarding any effects on milk production. These are conducted when there may be concern for drug accumulation (i.e., long half-life).
3. Mother–infant pair: Mother and infant provide blood to determine drug concentrations and pharmacokinetics in the lactating woman and infant as well as drug excretion in human milk. These studies can also include an assessment of the drug effects in the infants. These studies are typically done if there is evidence that there is substantial drug transfer into human milk placing the infant at risk.

FDA's clinical lactation studies guidance encourages sponsors to consider conducting clinical lactation studies even when not required, such as

1. when a drug under review for approval is expected to be used by women of reproductive age,
2. use of a drug in lactating women becomes evident after approval,
3. the sponsor is seeking a new indication for an approved drug and provides evidence of use or anticipated use of the drug by lactating women, and
4. when marketed medications are commonly used by women of reproductive age (FDA, 2019a).

Although the lactation guidance is relatively thorough in outlining research considerations for types of lactation studies and ethical considerations for the participation of lactating women in clinical studies, the guidance falls short in many of the same ways the pregnancy guidance does. First, although lactation studies are encouraged, FDA guidance does not set clear expectations or timelines for when these studies should be completed. Further, as with the guidance on pregnancy, FDA guidance on lactation recommends follow-up examination and testing of the breastfed infant in clinical studies of approved medications postmarket, but it does not provide details on expectations for the duration of follow-up and what types of outcomes should be measured. Nor does it provide guidance on the continuum of care from pregnancy to lactation and consideration for breastfeeding if enrolled in a clinical trial while pregnant.

For studies of new investigational products, FDA guidance on lactation dissuades lactating women from continuing to breastfeed, which could have detrimental health effects on the children receiving human milk, could affect their milk supply, maternal–infant bonding, and could be considered a harm in and of itself. While the mother may express milk to maintain her milk supply, particularly for a short-term study, the discontinuation of breastfeeding presents a major barrier for studies of medications to treat conditions not specific to breastfeeding as well as breastfeeding conditions, such as mastitis, low milk supply, or breastfeeding-associated pain. Discontinuation of breastfeeding and the resultant increased risk of infectious disease and other morbidities may outweigh the potential (and likely low) risk of the investigational product. Human milk transfers beneficial bacteria, immune cells, and nutrients to the nursing child that improve the immunological health of the child (Camacho-Morales et al., 2021).

Patients seeking treatment for breastfeeding conditions typically want to continue breastfeeding. In most cases, requirements to discontinue breastfeeding are not scientifically justified. One common method for estimating the risk of drug exposure to the child is the estimate of the relative infant dose (RID), which standardizes the exposure by weight. A RID of less than 10 percent is generally considered safe for use in lactation and safe for breastfeeding the healthy child (Newton and Hale, 2015). Currently, approximately 90 percent of marketed drugs have a RID in the "acceptable" range considered safe for breastfeeding (less than 10 percent). Therefore, these restrictions present sometimes overly burdensome barriers for participants in these studies and create challenges with recruitment for these studies, as suspending breastfeeding to participate in a study may dissuade many potential research participants from enrolling.

Further, when the study protocol calls for the cessation of breastfeeding, there is no requirement to provide participants with any alternatives

or remuneration (i.e., pumping supplies, free formula for supplementation) to offset the monetary and potential emotional costs of discontinuation requirements. This may place an undue burden and greater barriers to entry for low-income populations. Lastly, FDA guidance on lactation suggests sponsors consider conducting an assessment on the effect of the product on milk production, which may include both volume and composition. However, the guidance provides few details on how this assessment might be conducted or how this assessment may take into account the different stages of breastfeeding.

FDA Rule on Labeling for Pregnancy and Lactation

In 2014, FDA amended its regulations through the finalization of its Pregnancy and Lactation Labeling Rule (the PLLR) (initially proposed in 2008), which created a consistent format for providing information about the risks and benefits of prescription drug and biological product use during pregnancy and lactation and by females and males of reproductive potential. For human prescription drug and biological products approved on or after June 30, 2001, the PLLR required that the labeling be revised to include

1. a summary of the risks of using a drug during pregnancy (Section 8.1 of the labeling) or lactation (Section 8.2 of the labeling), and for females and males of reproductive potential (Section 8.3 of the labeling);
2. a discussion of the data supporting that summary; and
3. relevant information to provide health care providers and patients with the best available evidence to make informed decisions regarding the use of medications during pregnancy and lactation.

Under the PLLR, both the pregnancy and lactation sections of a drug or biological product's labeling must include summaries of the pertinent available evidence providing information about the safety and use of the drug in pregnancy and lactation. Information on pregnancy exposure registries, if available, including how to enroll or to obtain more information, must also be included. A risk summary is also required that provides, as a narrative summary, a statement of background risk if there are data demonstrating that the product is systemically absorbed or if there are data on the product's presence in human milk. This includes a separate summary based on human data, animal data, and pharmacologic data that describes the risk of adverse developmental outcomes, if such data are available (FDA, 2018b).

Additionally, the PLLR requires statements acknowledging when data on any of the labeling requirements are not available or do not establish the presence or absence of drug- or vaccine-associated risk.[5] Lastly, the PLLR requires the label to be updated to include clinically relevant information as it becomes available to prevent the label from becoming "inaccurate, false, or misleading."[6]

Although the PLLR was designed to provide more relevant summary information for health care providers and patients, there still is not much information in product labels about their use during pregnancy or while lactating. A cross-sectional labeling analysis of 290 newly FDA-approved medications from January 2010 to December 2019 indicated that

> All products submitted after June 20, 2015, were in compliance with the Pregnancy and Lactation Labeling Rule (PLLR); however, of those submitted between 2010 and 2015, 32.6 percent were not in PLLR format by the designated date of June 30, 2019. Human data on pregnancy and lactation were available in less than 20 percent of new product labeling. (Byrne et al., 2020)

Postmarketing Commitments and Requirements

Phase IV postmarketing studies are commonly required by FDA (2016). These are clinical studies, epidemiologic studies, and registries that focus on specific questions of safety and/or effectiveness for various related conditions of the disease of interest for related demographic populations, such as pediatrics (FDA, 2023c), related diseases, special populations, safety issues, and long-term use. These studies are known as postmarketing commitments or postmarketing requirements. Postmarketing commitments involve preclinical studies or clinical trials that a sponsor agrees to conduct postapproval but are not legally required to be performed (FDA, 2016). Postmarketing requirements, however, are preclinical studies or clinical trials that a sponsor is required to conduct in order to comply with certain laws and/or regulations, or to assess a known serious risk related to the use of the drug, assess signals of serious risk related to the use of a drug, or identify an unexpected serious risk when available data indicate the potential for a serious risk (FDA, 2016). FDA may also impose postmarketing requirements on manufacturers of certain Class II or Class III medical devices that are approved by FDA.

[5] *Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b),* 21 CFR § 201.57(c)(9).

[6] *Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b),* 21 CFR § 201.57(c)(9).

Data for these types of studies can come from institutional electronic medical records, health insurance claim data, and registries. These observational studies may aid in (1) assessing the relative risk of a serious adverse event occurring with the use of a particular drug or biologic, (2) identifying certain risk factors that make the occurrence of a serious adverse event among a particular patient population more likely, and (3) obtaining data over a significant period of time, which may help identify rare serious adverse events, among others (FDA, 2011). Observational studies of pregnancy may aid in informing pregnancy or child outcomes following drug exposure, in comparison to a group that has not been exposed to the drug product (FDA, 2011).

FDA has the authority to require postmarketing studies and clinical trials to (1) "assess a known serious risk related to the use of the drug," (2) "assess signals of serious risk related to the use of the drug," and (3) "identify an unexpected serious risk when available data indicate the potential for a serious risk."[7] FDA also has the authority to require postapproval studies or trials if it becomes aware of new safety information (FDA, 2011). However, if human pregnancy or lactation data has not been collected at the time of FDA approval, FDA may not have the information required to determine whether there are potential risks to pregnant and lactating women to evaluate through postmarketing studies. Expanding FDA's authority to request postmarketing studies could help fill important clinical knowledge gaps on the safety and efficacy of products in pregnant and lactating women, particularly to better identify long-term effects of a product.

Section 505(o)(3)(E)(ii) of the FD&C Act requires a sponsor to "periodically report," and in any event at least annually, on the status of preclinical studies or clinical trials, regardless of whether or not the sponsor was required to conduct a clinical trial or study as part of a postmarketing requirement or voluntarily chose to do so. A sponsor must report on the preclinical study or clinical trial's status to comply with this section.[8] The status report must include a timetable for the completion of specific target goals, along with a status update of the study or trial (FDA, 2011). Unfortunately, the annual reports do not provide details on the ongoing status of the trial such as enrollment updates, any adverse events reported to FDA, or any information that might assist health care providers make prescribing decisions, although any adverse events that inform the labelling should be reflected in the label under FDA requirements.

[7] *New Drugs,* 21 USC § 355(o)(3)(B).
[8] *New Drugs,* 21 USC § 355(o)(3)(E)(ii).

In 2019, FDA issued its draft guidance, "Postapproval Pregnancy Safety Studies." This guidance describes three postapproval approaches to assessing drug safety in pregnant women who have been exposed to a drug or biological product: (1) pharmacovigilance; (2) pregnancy registries; and (3) complementary data sources (FDA, 2019b).[9] Based on an approach's relative strengths and limitations and its potential application to a particular drug or biological product, FDA may recommend or require a particular approach or combination of approaches to be used by a sponsor for a particular drug or biologic product (FDA, 2019b).

Pharmacovigilance

The goal of pharmacovigilance is "to protect patients from unnecessary harm by identifying previously unrecognized drug hazards, elucidating predisposing factors, refuting false safety signals, and quantifying risk in relation to benefit" (Talbot and Nilsson, 1998). Pharmacovigilance takes place throughout the life cycle of the pharmaceutical product, including the entire drug development pathway and postmarketing surveillance.

Pharmacovigilance has three core functions: case management, signal management, and risk–benefit management (Beninger, 2020).

1. Case management is concerned primarily with the input of adverse event information. Such information is collected throughout all stages of a product's life cycle, including all phases of product development, and filed into relevant safety databases in a standardized way and reported to pertinent regulatory authorities in a timely way to meet compliance requirements.
2. Signal management is concerned with querying the safety database to answer internal sponsor questions and external regulatory agency issues in light of newly available safety information. Although signal management can be done prior to product approval, the importance of signal management increases significantly postapproval, with the growth of the patient population exposed to the product.
3. Benefit–risk management is concerned with maintaining a favorable benefit–risk balance across the range of patient populations and labeled uses through the appropriate use of labeling categories and other related regulatory and administrative mechanisms (Beninger, 2020; FDA, 2023a).

[9] The three postapproval approaches can be used alone or in combination with each other.

As pointed out in the FDA guidance, individual case safety reports are the most common source of reports of adverse pregnancy outcomes, but they can be challenging to interpret owing to incomplete information or additional risk factors for the adverse event, which might not be addressed in the case report (FDA, 2019b). Further, FDA guidance notes there are limitations to spontaneous marketing reports, including underreporting, lack of a denominator, and incompleteness of reported information. Therefore, FDA guidance recommends using additional sources to evaluate product safety, such as observational studies.

Pregnancy Registries

Pregnancy registries are a common study design that may be used to collect safety data in the postapproval setting and can help inform decision making among health care providers and their patients (FDA, 2023e). Pregnancy registries involve the prospective enrollment of women who have been exposed to a drug or biologic product and are usually followed through delivery and postpartum to evaluate the effects of exposure on the newborn (FDA, 2019b). Such registries may be led by sponsors, government, or institutions; they can be product specific or cover multiple products; they can also involve multiple institutions and other collaborative stakeholders and include more than one country. Registries are an important and potentially powerful safety tool because of their ability to prospectively capture detailed patient data over a long period of time (FDA, 2019b). Because of difficulties in enrollment and retention, however, pregnancy registry data often may not provide sufficient statistical power to assess the safety of drug and biological products during pregnancy (FDA, 2019b).

A large portion of the draft guidance "Postapproval Pregnancy Safety Studies" discusses recommendations for the design and implementation of pregnancy registries. Pregnant women who have been exposed to a drug or biological product may volunteer to participate in a registry during their pregnancy and be followed through delivery (FDA, 2019b). Because a pregnancy registry follows a pregnant woman over the course of their pregnancy and following the birth of their newborn, it may allow assessment of "maternal, obstetrical, fetal, and infant outcomes, including pregnancies that do not result in a live birth" (FDA, 2019b). Although the guidance points to a number of strengths in using pregnancy registries, it highlights some limitations for such registries: analyses may result in insufficient statistical power in detecting associations for rare pregnancy outcomes, registries may not address more specific or rare congenital malformations or congenital anomalies, there may be significant challenges to recruitment and retention, and the data from a registry alone may not be

able to adequately assess the safety of a drug or biological product taken during pregnancy (FDA, 2019b).

FDA also provides guidance on the potential duration of a pregnancy registry. It recommends that pregnancy registries collect data until there is sufficient information gathered to meet the registry's scientific objectives; conversely, if the registry is not able to collect sufficient information to meet its objectives, consideration should be given to discontinuing the registry (FDA, 2019b).

FDA may also require that a lactation study be added to a pregnancy registry to capture potential drug exposure data during breastfeeding (FDA, 2019b). Such lactation data are gathered to assess the safety of drugs and biological products that women may take while breastfeeding, which may or may not have been taken while pregnant (FDA, 2019b). While there is a human milk research biorepository that evaluates the transfer and effects of medication in human milk (Mommy's Milk, 2024), there appear to be no existing lactation-specific registries.

Complementary Database Studies

FDA guidance on postmarketing studies also discusses complementary studies that may be conducted alongside pregnancy registries to address the "specific effects" of a drug or biological product during pregnancy (FDA, 2019b). These studies may be retrospective in their design and use secondary data sources, such as electronic health records, population-based surveillance, and national registries or registers.

For studies that use electronic health care data, FDA provides recommendations for identifying pregnancies in health care records and acknowledges the challenges of identifying pregnancies that do not result in a live birth. The ability to link the records of the pregnant woman to the offspring is critical to evaluating fetal outcomes related to in utero exposure (Johnson et al., 2013). These linkages can be developed through a number of records, including birth certificates, health record identifiers, and congenital malformation surveillance registries. The guidance also describes methods for estimating gestational age to understand the window during which a fetus would have been exposed to a medical product used by a pregnant woman.

Another form of complementary studies are case-control studies, which can be useful for obtaining additional information or long-term follow-up once a safety signal has been identified. While the guidance notes that these studies can be affected by recall bias from self-reported outcomes, case-control studies have the benefit of being able to capture detailed exposure and outcome assessments through follow-up interviews with the pregnant individual and to collect biospecimens.

FDA guidance outlines the necessary considerations and the existing challenges for selecting and validating cases and matched controls to be included in the analysis. FDA goes on to note that it is important for cases and controls to be from the same disease population whenever possible to facilitate comparisons.

In addition, FDA has made a number of commitments in the Prescription Drug User Fee Act (PDUFA) VII Commitment Letter that focuses on pregnancy postmarketing requirements. As described in Box 3-2, these initiatives will result in updated guidance for sponsors conducting postmarketing studies with pregnant women.

REDUCING HARM THROUGH FEDERAL PROTECTIONS FOR HUMAN SUBJECTS

The Federal Policy for the Protection of Human Subjects outlines basic provisions for the oversight, ethics review, and approval of research with human participants. In 1991, it was revised and codified by 15 federal departments and agencies, and became known as the "Common Rule." Research funded or conducted by HHS is subject to additional regulatory protections, including provisions specific to the conduct of research involving pregnant women. HHS regulations for the protection of the rights and welfare of human participants in research are codified in title 45 of the *Code of Federal Regulations*, part 46, including Subparts A through E. Subpart A is the codification of the Common Rule. Subparts B, C, and D provide rules for specific subpopulations in research funded or conducted by HHS. Subpart B provides additional protections for pregnant women, human fetuses, and neonates; Subpart C provides additional protections for incarcerated populations; Subpart D provides additional protections for children; and Subpart E covers registration of IRBs with HHS (HHS, 2022a).

Under the requirements of Subpart B, pregnant women or fetuses may be involved in research if all of the following conditions are met:

- Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.

BOX 3-2
FDA's PDUFA VII Commitments

The Prescription Drug User Fee Act (PDUFA) was first passed by Congress in 1992. The law allows FDA to collect fees from drug manufacturers in order to fund the new drug approval process. It has been reauthorized six times, most recently in 2022. This seventh iteration of PDUFA is referred to as "PDUFA VII," and it extends PDUFA from fiscal year 2023 through fiscal year 2027. The law requires FDA to hold discussions with the regulated industry and public stakeholders, and to develop a "commitment letter" or "goals letter" that outlines FDA's performance and procedural goals for the time period of reauthorization.

One section of the PDUFA VII Commitment Letter focuses on optimizing the Sentinel Initiative (an electronic system for monitoring drug safety) in order to address questions of product safety and advance the use of real-world evidence for studying effectiveness. Within this section is a subsection on pregnancy safety in which FDA lays out a three-part plan for using postmarketing data to inform labeling on the safety of use during pregnancy, and to detect or evaluate safety signals in a timely manner. First, FDA commits to developing a framework describing how data from different types of postmarketing pregnancy safety studies can best be used. To do so, FDA will review published literature, hold a public workshop, and publish a workshop report describing the framework. The second step of FDA's commitment to improving pregnancy safety involves conducting demonstration projects to address gaps in knowledge about different study designs. FDA lists five specific assessments to be conducted, including:

1. Assess the performance of pregnancy registries versus electronic health record (EHR) database studies in detecting a safety signal when the medication is relatively common during pregnancy.
2. Assess the performance of single-arm safety studies versus signal identification methods using EHR data in detecting a safety signal when the medication is relatively uncommon during pregnancy.
3. Assess the performance of pregnancy registries versus EHR database studies in evaluating a safety signal when the medication is relatively common during pregnancy.
4. Assess the performance of major medical malformations as a composite outcome in signal detection and evaluation when there is a true risk for some but not all specific malformations.
5. Assess the performance of an algorithm using EHR and claims-linked data for pregnancy-related outcomes after use of vaccines in pregnant women.

Based on the results of these demonstration projects, FDA commits to updating the proposed framework and developing guidance to implement a standardized process for determining the necessity and type of pregnancy postmarketing commitments and requirements. The workshop report and initiation of demonstration projects are to be completed by September 2024, and FDA guidance is to be completed by September 2027.

- Any risk is the least possible for achieving the objectives of the research.
- If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then informed consent of the mother is required.
- If the research holds the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is required. The father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, temporary incapacity, or the pregnancy resulted from rape or incest.
- Each consenting individual is fully informed regarding the reasonably foreseeable effect of the research on the fetus or neonate.
- For children who are pregnant, assent and permission are obtained in accord with the provisions of Subpart D.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- Individuals engaged in the research will have no part in determining the viability of a neonate.

Subpart B is an important factor for the conduct of research involving pregnant women and is discussed in greater detail in Chapter 4. HHS regulations for human subject protections do not specifically address considerations for lactating women, nor do they clarify whether Subpart D, additional protections for children, apply when a child is exposed to the milk of a lactating woman participating in clinical research.

Despite this regulatory ambiguity, the Secretary's Advisory Committee on Human Research Protections (SACHRP) released recommendations in 2022 that address the protection of nonsubjects from research-related harms (HHS, 2022c). SACHRP acknowledges that IRBs vary in whether breastfeeding children of lactating research participants are themselves considered research participants—a determination that would require the application of Subpart D, which pertains to research with children. Even in circumstances when the IRB does not consider breastfeeding children of lactating research participants to themselves be research participants, SACHRP recommends that IRBs consider the risks to such children as nonsubjects who may be at risk because of their direct physical contact with the research participant.

FDA has not adopted the HHS regulations but has its own regulations for the protection of human subjects and institutional review boards.[10,11] While FDA's human subject regulations are not identical to those from HHS, they are similar (FDA, 2018a). Additionally, FDA released a proposed rule in 2022 that would harmonize certain sections of FDA's regulations on the protection of human subjects and IRBs with HHS regulations.[12] 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 among its membership individuals with relevant expertise if they regularly review protocols that include pregnant women.

FDA regulations for the protection of human subjects do include considerations specific for children (Subpart D), which FDA notes do apply when an infant is exposed to the milk of an individual enrolled in a clinical lactation study (FDA, n.d.a). However, in some contexts, IRBs may determine that collection of outcome data for the breastfeeding children of a lactating research participant does not constitute research, and that under either HHS or FDA definitions,[13,14] FDA and HHS regulations specific for children therefore do not apply (HHS, 2022c). In such cases, SACHRP also recommends IRBs consider the risks to breastfeeding children as nonsubjects. For postmarket lactation studies where breastfeeding is permitted, it is important that children are monitored for adverse events and that these data are collected and reported.

Office for Human Research Protections (OHRP)

The HHS Office for Human Research Protections (OHRP) was established in 2000 to oversee HHS efforts to protect human research participants in clinical research and to provide leadership for all federal agencies that support human subjects research under the Common Rule (HHS, 2020). OHRP's core functions include providing regulatory guidance and clarity, developing educational materials, administering IRB registration programs, and maintaining regulatory oversight of IRBs. OHRP's guidance documents are not legally binding but help to inform and guide IRBs. OHRP has several guidance documents addressing populations mentioned in HHS regulations for the protection of the rights and welfare

[10] *Protection of Human Subjects,* 21 CFR 50.

[11] *Institutional Review Boards,* 21 CFR 56.

[12] *Protection of Human Subjects and Institutional Review Boards,* 87 Federal Register 58733, (Sep. 28, 2022).

[13] Definitions, 21 CFR 50.3.

[14] Definitions, 45 CFR 164.501.

of human participants in research, including children and prisoners, but it has not issued any guidance on pregnant and lactating women as research subjects.

OHRP could develop guidance focused on pregnant and lactating women, including guidance to IRBs on the interpretation of Subpart B for clinical research including pregnant women and the applicability of Subpart D for clinical research including lactating women in which the child is exposed to human milk. Various research institutions have developed guidance and standard operating procedures specific to clinical research including pregnant women (CU Denver, 2022; MCW, 2023; Purdue, 2019; University of Utah, n.d.; UW, 2021, 2023). A study at the University of Washington found that such materials facilitated research that includes pregnant women at the institution (Mastroianni et al., 2020). OHRP guidance applicable to the inclusion of pregnant and lactating women in clinical research could help IRBs provide feedback to protocols and ultimately approve more protocols for human subject research involving pregnant and lactating women.

SACHRP was created in 2003 to "provide expert advice and recommendations to the Secretary [of Health and Human Services], through the Assistant Secretary for Health, on issues and topics pertaining to or associated with the protection of human research subjects" (HHS, 2022b). SACHRP is composed of appointed experts and heads of various HHS agencies. As a committee, it provides advice on improving protections for research participants. SACHRP occasionally establishes subcommittees that are formed of experts on special topics of interest to the committee (HHS, 2016). For example, in the early 2000s, SACHRP created a subcommittee to provide advice on pediatric research "to help ensure that children who participate in research are neither underprotected nor overprotected" (HHS, 2016). To date, there is no record that SACHRP has provided advice on the inclusion of pregnant and lactating women in clinical trials. It does have the authority to establish a subcommittee focused on research with pregnant and lactating women and to request recommendations for HHS to ensure that pregnant and lactating women included in research are similarly neither underprotected nor overprotected.

Institutional Review Boards

Federal regulations require that institutions engaged in clinical research involving human participants must use an IRB (HHS, 2018). IRBs are tasked with determining whether the research protocols before them are ethically justifiable and with ensuring that the researchers involved are not bound to certain interests that might pose a conflict with the ethical conduct of the research (Grady, 2015). Importantly, IRBs also serve a

critical role in interpreting federal and state laws and regulations relevant to the protection of human subjects from exploitation and undue risk of harm. As a result, IRB members must be familiar with the Common Rule, FDA, HHS, and other agency and department regulations on human subject protections, as well as OHRP guidance. Given that IRBs are responsible for promoting a favorable balance of risks and benefits to research participants and that there is regulatory ambiguity for the protection of pregnant and lactating participants (van der Zande et al., 2017), clearer guidance from OHRP could help IRBs uphold their duties to minimize harm to pregnant and lactating participants.

For an institution to receive federal support for research involving human subjects, it must register its IRB with OHRP and renew its registration every 3 years to ensure compliance with federal regulations. IRBs that review HHS-supported research must apply the Common Rule and other HHS regulations for the protection of human subjects to that research, including those addressing the inclusion of pregnant research participants. In addition, IRBs that review FDA-regulated research must apply FDA regulations for the protection of human subjects to that research, which are similar but not identical to the Common Rule.

In ensuring compliance with federal regulations, IRBs aim to ensure that the research is conducted ethically, which includes minimizing harm to research participants and balancing risk with commensurate benefit to the research participants or the broader population through the creation of generalizable knowledge. It also ensures that informed consent is adequate and that there is equitable selection of research participants.

REDUCING HARM THROUGH RESEARCH DESIGN

Postmarket observational studies are informative, but they delay the generation of safety data for pregnant and lactating women until the product is already being broadly used by the public, thus amplifying the potential for harm. To move beyond a reliance on such data, consideration of how to reduce harm to research participants through research design is important (Huybrechts et al., 2019). Such research can be done safely and ethically, but as noted earlier in the chapter, FDA draft guidance relevant to clinical research in pregnant and lactating women provides few details on the appropriate design of these studies. The design and methods of a study are a crucial element of reducing harm to research participants (IOM, 2003). Research on human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) is one area that has had success in conducting clinical research with pregnant and lactating women, as described in Box 3-3. Although there are still improvements to be made to HIV/AIDS research involving pregnant and lactating

BOX 3-3
Successes of HIV Research in Pregnant and Lactating Women

HIV/AIDS is among the most serious diseases confronting pregnant, potentially pregnant, and lactating women. It is also one of the few areas of human research where there is considerable experience conducting research involving pregnant and lactating women (HHS, 2023). While it unquestionably represents an example of the successful conduct of clinical trials in pregnant and lactating women, it also offers significant lessons for research involving pregnant and lactating women going forward.

In 1987, FDA approved the first treatment for AIDS, the antiretroviral therapy zidovudine, known as AZT. Pregnant people living with HIV were excluded from the studies supporting approval. Health care providers and pregnant patients faced a stark decision: to use AZT to attempt to prevent transmission of HIV to the fetus or to stall treatment during pregnancy owing to the uncertainty of the risks to the fetus but potentially worsening the progression of AIDS in the pregnant individual. For AZT, health care providers, scientists, and AIDS advocacy groups (notably ACT-UP, the AIDS Coalition to Unleash Power), the National Institutes of Health, and others were ultimately successful in overcoming reservations about potential harms from in utero exposures during research. In 1994, results from Protocol 076 were published, finding that AZT was safe and effective for preventing vertical transmission and paving the way for pregnant women to have greater access to the life-saving medication (Connor et al., 1994).

In 1998, once the risk of HIV transmission to the infant through human milk was established, the study of the safety and efficacy of antiretroviral drugs (ARVs) for preventing transmission became a priority (UNAIDS and WHO, 1998a). Clinical trials to evaluate the use of AZT, combination AZT and Lamivudine, and Nevirapine to prevent transmission through human milk were already underway at this point (UNAIDS and WHO, 1998b).

The only antiretroviral therapy licensed for use in pregnancy is AZT in the third trimester (Chilaka and Konje, 2021). In the meantime, newer, safer, and more effective ARVs have been approved for use in the general adult population. Efforts to prevent perinatal and postnatal transmission of HIV have contributed to an evidence base for the use of established ARVs during pregnancy and lactation. The study of newer ARVs during pregnancy and lactation have led to the development of clinical guidelines that support their use in pregnancy and while breastfeeding to prevent perinatal and postnatal transmission, respectively (HHS, 2023). While ARVs are among the most studied products in pregnancy, challenges remain. The median time from FDA approval to first published pharmacokinetic (PK) data to guide safety and dosage in this population has been calculated to be 6 years, with a range of 2–14 years (Colbers et al., 2019). Moreover, pregnant women continue to be excluded from trials studying newer ARVs as well as preexposure prophylaxis, a preventive medication (PHASES Working Group, 2020).

Among the lessons learned from doing HIV research in pregnancy and lactation is how to design and conduct clinical trials that are ethical, feasible, and acceptable to the participants and affected communities, even in the presence of concerns for liability conducting the research (Cohen, 1992; Lyerly et al., 2021; Penazzato et al., 2022). Researchers and IRBs gained expertise in, and became comfortable with, the idea that clinical research including pregnant and lactating woman presents

BOX 3-3 Continued

more than just risks of harm, but importantly it presents the prospect of benefits that can extend well beyond the research participants by means of generalizable knowledge and improved public health outcomes (Little et al., 2016). This includes a recognition that the treatment and prevention of a pregnant woman's disease can offer the prospect of benefit to the fetus.

There is also growing awareness of the need to broaden the research agenda to prioritize not only the health of the fetus but also the health of the pregnant woman (Little et al., 2016). As the need to conduct clinical studies in both pregnant and lactating people was recognized, research infrastructure was developed—including the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Network and the Antiretroviral Pregnancy Registry—providing people living with HIV, clinicians, and researchers greater access to the research.

women, the lessons learned from HIV/AIDS can inform broader research involving pregnant and lactating women.

Staging of Clinical Research

An important consideration for designing clinical studies that include pregnant and lactating women is the timing of enrollment of these populations. Regulators and sponsors must strike a balance between including pregnant and lactating women in a sufficiently timely manner as to provide quality evidence on the use of the product in these populations, without rushing their inclusion in the absence of adequate safety information or planning. Moreover, a potential form of harm resulting from the inclusion of pregnant and lactating women in clinical research is that FDA approval of a medical product could be delayed, slowing the general population's access to the product. Delays in regulatory approval could result from more complex data analyses and identification of false-positive safety signals, which are discussed in more detail in Chapter 5. Considering the most appropriate stages of clinical development to include pregnant women and lactating women (likely different for each population, given the differences in risk) could mitigate the risk of this form of harm. Importantly, the committee emphasizes that it is possible to include pregnant and lactating women in clinical research without expanding the risk of harm from delayed product approval, but careful consideration for which staging approach fits the research needs of the project being conducted is important. Nothing in current FDA regulations or the committee's recommendations would require clinical studies in pregnant and lactating women to be complete before product approval for the general adult population.

A staggered approach to the enrollment of pregnant and lactating women entails conducting PK/PD clinical studies specific to the population of interest concurrently with the conduct of Phase III trials in the general adult population (Eke et al., 2019). Staggered enrollment would allow for the development of study protocols specific to pregnancy and promote the involvement of researchers with expertise in conducting research in these populations (Baylis and Halperin, 2012). Enrollment of pregnant participants could also be tailored to begin recruitment with individuals in their third trimester of pregnancy, when fetal organogenesis is complete, gradually enrolling participants in earlier stages of pregnancy. Lactating women could be included earlier than pregnant women for investigational products, especially since FDA guidance suggests that women cease breastfeeding for investigational products. Therefore, there is no risk to the baby and lactating women could be enrolled earlier in the trial. However, to avoid breastfeeding cessation, single-dose PK studies, where human milk is collected at time intervals until the drug has been excreted from the body, could be done early to determine potential for infant exposure. Once these single-dose PK studies are completed, if the medication is deemed safe for breastfeeding, as is the case for 90 percent of on-market medications, then breastfeeding could continue.

In embedded enrollment, the strategy would involve enhanced safety and pharmacokinetic evaluations in pregnant and lactating women who enroll in Phase III or late Phase II studies for the general adult population (Eke et al., 2019). According to this approach, pregnant and lactating women would be evaluated as subpopulations of the broader adult population enrolled in the clinical trials. Because pregnant and lactating women would be enrolled in Phase II or Phase III trials, researchers would be able to collect data relevant to these phases of research simultaneously with the basic safety data being collected (Baylis and Halperin, 2012). An embedded approach to enrollment would also facilitate comparisons between pregnant or lactating participants and nonpregnant or nonlactating participants enrolled in the same trial.

A potential concern with this approach is that embedding pregnant and lactating women in the same trials as the general adult population could delay interpretation of overall trial results when there are challenges with the recruitment of pregnant and lactating participants, which could delay drug approval. It may also present risks to pregnant populations, given that there may not be sufficient safety and efficacy data before enrolling them in the trial. Therefore, this approach may be best for life-saving medications for conditions with no available alternative therapies, but not for non-life-threatening acute and chronic conditions for which alternate therapies are available.

The opportunistic approach to enrollment is a useful way of collecting data on pregnant and lactating women who become pregnant while already enrolled in a trial (Eke et al., 2019). Once the participant is unblinded and reconsented, pharmacokinetic and safety data can be collected for these individuals before therapy is discontinued and potentially throughout all trimesters of pregnancy and postpartum. However, an opportunistic enrollment approach is likely to be slow, and may not accomplish recruitment goals while clinical trials are actively being conducted. Such an approach also raises issues of whether the investigators involved in these trials will have sufficient expertise in pregnancy and lactation. Regardless, an opportunistic approach to enrollment can be an effective strategy for collecting data on the use of the product in early stages of pregnancy.

Pragmatic Study Designs

A pragmatic study design, specifically when focusing on pregnant and lactating women as the study population, is pivotal in advancing the understanding of medical products within real-world clinical settings (Eke et al., 2019). At their core, pragmatic study designs aim to evaluate the real-world effect of interventions or strategies that are already part of clinical practice (Patsopoulos, 2011; CU Denver, 2019). Unlike traditional clinical trials with tightly controlled settings, these studies strive to replicate the conditions encountered in routine patient care. This fundamental difference is crucial for gauging how interventions perform when applied to diverse groups of pregnant and lactating women during their specific health care journeys, which can be particularly useful in reducing harm in real-world use of the product (Eke et al., 2019).

One of the defining features of pragmatic trials in this context is the inclusion of a diverse and representative range of participants (Eke et al., 2019). By encompassing such diversity, pragmatic studies can provide valuable insights into how interventions function across different subgroups, considering such factors as age, ethnicity, socioeconomic status, and underlying health conditions, which often influence health care outcomes.

Pragmatic study designs in pregnant and lactating women would be bolstered by encompassing longitudinal data collection. Recognizing that pregnancy and lactation are dynamic processes with evolving needs and experiences, these trials could span extended periods to capture a comprehensive view of the effects of the intervention over time. This longitudinal approach enables researchers to assess not only short-term outcomes but also the sustainability and long-term effect of the intervention. Observing the long-term effects of medical product exposure can facilitate the identification of latent adverse effects. In addition, pragmatic

study designs are attuned to minimizing disruptions to routine clinical care (CU, Denver, 2019). This consideration is essential to ensure that both pregnant and lactating patients and health care providers can participate in the study without an undue burden or disruption to their usual health care activities. By integrating seamlessly into clinical practice, pragmatic trials can gather data in a nonintrusive manner that respects the demands of health care delivery.

Opportunistic Studies

Nonrandomized opportunistic studies, a subset of observational research, provide a unique way to study pregnant and lactating women already using specific medical products or interventions (Sheffield et al., 2014). Opportunistic studies thus reduce harm to research participants by only studying the product in individuals who would already be using the product. However, conducting such studies requires careful consideration to ensure ethical and appropriate practices, with informed consent and IRB oversight being ethical cornerstones. Participants must fully understand the research objectives, potential risks, and benefits. An opportunistic study could be a useful study design when it would otherwise be ethically or logistically challenging to conduct an interventional study, such as chemotherapy treatment during pregnancy.

Innovative Methodologies

In striving toward increasing research in pregnant and lactating women earlier in the drug development process, several innovative approaches can be undertaken to conduct and analyze such clinical research safely while lessening the risk of harm to the pregnant woman and developing fetus. Although many of these methods are still evolving, they present novel ways to evaluate the safety and efficacy of medical products before they are used in humans. Further exploration of these methodologies could align with FDA's Broad Agency Announcement for regulatory science innovation, advancing the ability of FDA regulators to assess clinical studies that use methods to predict exposure to the medical product under evaluation (FDA, 2024a). In fact, FDA recently funded a project studying the use of physiologically based pharmacokinetic models (FDA, n.d.b).

Fetal–Placental Transport

Innovative approaches that facilitate the understanding of the fetal–placental interface—a barrier that limits drug delivery to the developing

fetus—are important to predict fetal exposure to medical products in utero. Innovative techniques such as in vitro, ex vivo human cotyledon perfusion, placental drug transport-on-a-chip, and in silico models are increasingly being used to evaluate maternal–fetal medication transfer across the fetal–placental interface prior to human dosing during pregnancy to predict a drug's safety. These approaches represent promising methods for generating necessary data (Eke et al., 2020). Microengineered models of the human placenta (placental drug transport-on-a-chip models) are currently being used to simulate and explore drug transfer between the maternal–fetal circulation, with the goal of reducing the risk of fetal harm while conducting research safely (Eke et al., 2020). Further exploration of these technologies can enhance their predictive capabilities and have the potential to advance their readiness for use in regulatory decision making.

In Vivo Exposure Assessment Methods

The use of methods that minimize exposure to the medical product being studied, specifically microdosing and short-course (targeted) PK study approaches that have been increasingly employed, could generate early data for pregnant and lactating women (van Nuland et al., 2019). Microdosing involves administering a dose that stimulates a cellular response, but it is a small fraction of the dose that is anticipated to produce any therapeutic effect. Given the success of microdosing strategies in reducing drug development times for pediatric patients, this strategy may also be successfully applied to pregnant individuals (Burt et al., 2016).

Population Pharmacokinetic Modeling

A population PK analysis estimates standard values for PK parameters in a specified population (Avram, 2020). Population PK models are simultaneously capable of explaining interindividual variability, intraindividual variability, and variability attributable to demographic or clinical characteristics. A benefit of a population PK approach is that it involves collecting fewer samples from a larger study population, and it can incorporate data from various sources, even if the data are incomplete (Sheffield et al., 2014). Population PK modeling can be particularly useful for determining dosing in pregnancy after an initial PK study in a small group of research participants has indicated that pregnancy alters the PK of the medical product (Coppola, 2022). However, since it requires a larger number of subjects to complete the study, it is only realistic for common conditions with a large population taking the same medication during pregnancy.

Physiologically based Pharmacokinetic Modeling

Physiologically based PK (PBPK) models integrate preclinical and clinical data that have been collected to predict drug concentrations in multiple tissues following the administration of a medical product (Avram, 2020; Eke et al., 2021). These mathematical models are capable of producing reliable predictions of drug exposure in pregnant women and can account for the stages of pregnancy and drug–drug interactions, as well as predict any adverse effects of the drug (Eke et al., 2020). PBPK models also hold promise for predicting infant exposure to a drug through human milk. In addition, modeling can help predict the safety of exposing a child to the drug through human milk. However, PBPK models have so far been unable to reliably predict fetal PK parameters for in utero exposure (Eke and Gebreyohannes, 2020).

Human Milk Transport Modeling

Predicting drug exposure in human milk using in vitro approaches could help inform in silico models that simulate newborn exposure to a drug through human milk. Milk-to-plasma ratio of drugs—an important parameter in predicting breastfed drug exposure to a child through human milk—through passive diffusion and the directionality of drug transport have been studied using an in vitro mouse mammary epithelial cell culture model that mimics the secretory and tight-junction properties of human mammary epithelium (Eke et al., 2020).

CONCLUSIONS

Conclusion 3-1: The U.S. drug development regulatory process is designed to minimize harm for research participants and for those who use approved medical products. Pregnant and lactating women, as well as their fetuses and children, are not able to benefit from the harm minimization strategies that are incorporated into medical product development, review, and approval processes. This is because pregnant and lactating women are often excluded from clinical research, which leaves them and their health care providers with insufficient safety and efficacy data to make informed decisions about using medical products.

Conclusion 3-2: Current FDA guidance on clinical studies with pregnant and lactating women describes limited aspects of study design, research time lines, safeguards, and product-specific monitoring. Greater clarity and specificity of regulatory guidance for conducting research with pregnant and lactating women outside of postmarketing commitments would help further reduce and prevent harm for these populations.

Conclusion 3-3: Guidance from the Office for Human Research Protections (OHRP) on involving pregnant women, lactating women, and breastfeeding infants and children in clinical research could help inform institutional review boards on how to safely oversee this research, including how to interpret Subparts B and D of 45 CFR 46 and how to properly assess and reduce risk in clinical research that involves pregnant and lactating women and their offspring.

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4

Mitigating Liability Associated with Clinical Research

Chapter 3 outlines strategies to minimize harm in clinical research settings, which is an important factor in reducing potential liability in those trials and in the postmarketing clinical setting. This chapter discusses additional strategies that may mitigate liability for clinical research involving pregnant and lactating women for several key stakeholders in the research enterprise: industry sponsors, institutions, institutional review boards (IRBs), and investigators. It also discusses additional legal protections for pregnant research participants.

Pregnant or lactating research participants and their offspring who were harmed in clinical research are currently able to seek compensation from sponsors, research institutions, investigators, and IRBs through the tort system. However, the process of obtaining relief is arduous, time consuming, and inequitable. Significant uncertainty prevails, and the system neither satisfies people who have suffered injury nor stakeholders who worry about liability risks. Compensation schemes offer an alternative to the tort system. There are several different models of compensation systems used by institutions and organizations for those injured in clinical research. Each of these systems has varying degrees of coverage for injuries and has specific ways of how those injured can request compensation. Compensation schemes vary in the damages that they cover—examples include costs of medical expenses, pain and suffering, lost wages, and death. The compensation programs for research injuries discussed below include self-indemnity programs, agency-affiliated compensation programs, and certain types of federal no-fault compensation schemes, such

as the Countermeasure Injury Compensation Program (CICP). While the chapter presents some of their strengths and weaknesses, it does not make recommendations for each of these compensation strategies, but simply reviews the evidence for each.

MITIGATING LIABILITY FOR INDUSTRY SPONSORS

Drug development typically happens within industry, with more than 99 percent of products approved between 2010 and 2019 sponsored by for-profit entities and the majority of phased clinical trial costs coming from industry (Cleary et al., 2020; Zhou et al., 2023). Although the committee could not find a systematic review identifying funders of research with pregnant and lactating women and acknowledges that industry funding is the most difficult funding source to track (Moran, 2009), a review of funding disclosures in the published literature shows that the National Institutes of Health (NIH), the U.S. Agency for International Development, and the Bill and Melinda Gates Foundation make up the highest proportion of funders for maternal health research (Footman, 2014). Nonetheless, industry has an important role to play in advancing research and evidence in pregnant and lactating women. Industry sponsors confer with the U.S. Food and Drug Administration (FDA) and carry out the trial design for a product and are responsible for monitoring a trial throughout. Given their critical role in all aspects of clinical research, the committee considered potential strategies to mitigate industry sponsor liability.

FDA Regulatory Guidance

As covered in Chapter 3, FDA has issued several guidance documents relevant to conducting research in pregnant and lactating women that could be improved upon to minimize harm to these populations. One way to improve guidance documents is for FDA to provide additional detail and clarity. Stakeholders for activities at different stages along the product development pathway have identified the lack of regulatory clarity from FDA as a challenge to including pregnant and lactating women in research (NASEM, 2023). Uncertainty regarding what evidence FDA would consider adequate for studies including pregnant and lactating women and additional guidance for conducting studies on conditions specific to pregnancy or lactation is of particular concern for research sponsors. This uncertainty may stem from the lack of guidance from FDA on determining the safety and efficacy of a product in pregnant women through clinical studies. In fact, FDA's guidance on pharmacokinetics (PK) in pregnancy reads "This guidance . . . does not address ways to assess efficacy of a drug in pregnancy or how to assess whether the drug

causes adverse pregnancy or neonatal outcomes" (FDA, 2004). It may also stem from FDA guidance indefinitely remaining in draft form without finalization, leaving industry sponsors unsure if the draft truly represents the final word. FDA has not published a time line or set public goals for finalizing FDA guidance.

Although not legally binding, published guidance from FDA nonetheless sets expectations for product sponsors, clinical investigators, IRBs, FDA reviewers, and others involved in clinical research and review, as discussed in Chapter 3. Industry values guidance because it provides consistency in expectations for themselves and their competitors (Seiguer and Smith, 2005). If a lawsuit arises, clear FDA standards and evidence that the sponsor complied with those standards may support the sponsor's defense.[1] While compliance with federal regulations or guidance is generally not a complete defense, it can bolster the defense to be able to demonstrate compliance with detailed federal requirements or, to a lesser extent, recommendations, particularly when they leave little room for discretion on the part of the sponsor. For example, the *Third Restatement of Torts* states that a product's compliance with regulation and safety standards is considered when determining whether a product is defective (American Law Institute, 2023).[2]

Informed Consent

As outlined in Chapter 2, in addition to supporting ethical requirements, robust informed consent may provide some liability protection. This section discusses informed consent considerations that may mitigate liability for industry sponsors. Informed consent provisions to mitigate liability for institutions, IRBs, and investigators is discussed later in the chapter. Depending on state law, sponsors may be responsible for making sure that informed consent is appropriately documented and obtained. Careful attention to the information that is provided to investigators and the informed consent process may provide the best backstop to a claim based on failure to warn. Sponsors must take care to provide all the required information in the informed consent form in the investigator's brochure. FDA has specific guidance applicable to pregnant women that should be included. Special considerations for information on the

[1] As presented to the committee in open session by Kirke Weaver on June 16, 2023.

[2] The *Restatement of Torts* is a treatise issued by the American Law Institute that summarizes the general principles of common law in United States tort law. It is a consensus-based document and a secondary source of law that courts may adopt or cite as persuasive authority.

informed consent process provided to investigators in research with pregnant women include:

- Ensure that the investigator's brochure and the informed consent document outlines the known and potential risks associated with the investigational product. This should include any potential risks and the chance of unknown risks to an embryo or fetus, should a participant become pregnant.[3]
- For studies that may involve pregnant women, the investigator's brochure should include results of animal reproductive toxicity studies with appropriate explanation of their significance in humans.[4]
- If a participant becomes pregnant during a trial, unblinding should occur to determine exposure, and risks and benefits should be reviewed with the participant to determine whether it is in their best interest to continue treatment with the investigational drug (if they were on it). A second informed consent process appropriate for a pregnant participant should then take place. Whether or not they continue with the treatment, data should be collected (FDA, 2018).
- Consistent with FDA regulations, the consent document should be updated regularly as new safety information is obtained about the investigational product.[5]

Ensure Qualifications and Experience of Investigators and Clinical Staff

The selection of qualified investigators is a factor that can minimize harm and mitigate liability within clinical trials. Even if a product is performing as expected, research participants can suffer injuries because of negligence by the investigator. Although the injury may be caused by negligence, the sponsor may face some liability on the bases of negligent hiring, failure to properly vet investigators, or negligent training or supervision of trial sites (Medmarc, 2022). Investigators with training regarding the consent process and ongoing consent obligations as well as with training on the unique considerations and ethical issues related to research involving pregnant and lactating women may be more prepared to conduct studies with these populations. Sponsors can mitigate their liability

[3] 58 Fed Reg. 39408 (Jul. 22, 1993).

[4] *Revised Policy on Inclusion of Women of Childbearing Potential in Clinical Trials,* 58 Fed Reg. 39408 (Jul. 22, 1993).

[5] *Elements of Informed Consent,* 21 CFR 50.25(b)(5) (Jan. 27, 1981).

by carefully selecting experienced and well-trained or well-supervised investigators and by ensuring that all staff assisting with the conduct of the study are aware of their obligations in the safe conduct of the study.

Concerns about selecting qualified investigators is particularly critical for research involving pregnant and lactating women, given the complexity of conducting these trials. However, as discussed in Chapter 5, there is a lack of expertise among researchers, members of IRBs, institutional leaders, and other stakeholders in conducting research with pregnant and lactating women. Addressing this lack of expertise in research involving pregnant and lactating women can be an important factor in mitigating potential liability.

Clinical trial monitors may also be hired or engaged by sponsors to monitor the conduct of the trial, including data quality, informed consent procedures, safety of participants, and quality assurance (Love et al., 2022). Engaging monitors in rigorous external monitoring of clinical trials involving pregnant and lactating women may be another approach to mitigation of liability.

MITIGATING LIABILITY FOR INSTITUTIONS, IRBs, AND INVESTIGATORS

Most liability mitigation strategies proposed in previous reports have primarily focused on mitigating liability for sponsors. However, clinical research institutions of all types, IRBs, and investigators also have liability concerns that warrant consideration. Those concerns must be addressed for them to overcome their reticence to conduct or approve trials involving pregnant and lactating women. There are several liability mitigation strategies that could be considered.

Informed Consent

Although an earlier section in this chapter discusses the role of research participants' informed consent in mitigating liability for industry sponsors, this section provides an overview of steps in the informed consent process that reduces the risk that research institutions, IRBs, and investigators will be held liable for harm to participants. Under federal regulations, the clinical investigator has the main responsibility for providing and documenting each participant's informed consent. IRBs are responsible for determining the adequacy of the process design and the content of the consent form, and clinical research institutions are responsible for overseeing the process. Here, too, a carefully prepared plan governing the informed consent process can be a mitigating factor for liability. Unique regulatory considerations for informed consent in

research with women of childbearing potential and pregnant women include the following:

- The informed consent process must disclose potential risks and the chance of unknown risks to an embryo or fetus, should a participant be or become pregnant.[6]
- For studies that may involve pregnant women, informed consent should include a discussion in appropriate lay language about any completed animal reproductive toxicity studies and their significance for humans.[7]
- Subpart B of the U.S. Department of Health and Human Services (HHS) human research regulations, which provides additional protections to pregnant women, fetuses, and neonates in research, states that the individuals who provide consent for such research should be informed of the reasonably foreseeable effect on the fetus or neonate. Subpart B also requires that when research is conducted for the benefit of the fetus alone, informed consent must be obtained from both parents (though there are exceptions to the paternal consent requirement, as described in Chapter 3).[8] Ethical objections have been raised to the regulations that require paternal consent, especially because this rule for unborn fetuses is more burdensome than the rule in Subpart D (which contains provisions governing pediatric research), which requires dual-parent consent only for studies that offer no prospect of direct benefit to a born child and present greater than minimal risk (Little et al., 2018). As a practical matter, getting informed consent would make it unlikely that a father could succeed in objecting after the fact to the inclusion of the fetus in research that caused an injury. Nonetheless, the evidence needed either to support or to disprove this supposition is lacking because of the paucity of such research during pregnancy and the difficulty of knowing how many possible cases were resolved without a formal cause of action being brought.
- FDA regulations provide that if an IRB regularly reviews research involving pregnant women, the IRB must consider including one or more members who are knowledgeable about and experienced in working with this population.[9] Extending this paradigm, if

[6] *Precautions in Clinical Trials Including Women of Childbearing Potential,* 58 Fed Reg. 39411 (g) (Jul. 22, 1993).

[7] *Precautions in Clinical Trials Including Women of Childbearing Potential,* 58 Fed Reg. 39411 (g) (Jul. 22, 1993).

[8] *Research Involving Pregnant Women or Fetuses,* 45 C.F.R. 46.204.

[9] *IRB Membership,* 21 C.F.R. 56.107(a).

other IRBs and oversight bodies—such as expert consultants, data safety monitoring boards (DSMBs), radiation safety committees, or data security committees—are charged with reviewing the study protocol and its implementation, it may also be important for them to include among their membership individuals with knowledge and expertise in pregnancy.

- Special considerations may arise when the trial is expected to involve pregnant minors. Some states consider a pregnant minor as "emancipated"—that is, able to provide consent to medical care, among other legally binding contracts—a status that the minor often loses after delivery.
- Although not unique to research with pregnant women, HHS regulations require that for research involving more than minimal risk, the researcher must provide an explanation of whether any compensation or medical treatments are available if injury occurs and, if so, what such compensation consists of or where further information may be obtained.[10] It may be helpful to provide to research participants the information of the person or office that participants can contact should they experience an event that requires compensation. Investigators and their research teams must be made aware of the compensation process.

Self-Indemnity Programs

Indemnity is "a promise made by one party to another that it will cover any loss suffered by the other party" (International Society of Nephrology, 2022). One example of an institution using a self-indemnity fund for research-related injuries is the University of Washington (UW). Originally, UW purchased a commercial insurance plan to provide compensation for research-related injuries, which it had from 1972 to 1979. However, the cost in insurance premiums far surpassed the amount the university was paying in claims.[11] Therefore, in 1979, UW created a self-funded no-fault plan that covers up to $10,000 in out-of-pocket research-related injuries and up to $250,000 for care received at UW Medical Center (Henry et al., 2015).[12] The compensation collected in the university's indemnity pool is intended to provide necessary medical care to subjects who sustain a bodily injury directly from participation in a research project or trial funded by UW (Henry et al., 2015). Although the committee was not able to access information on the number of claims, the Director

[10] *General Requirement for Informed Consent,* 45 CFR 46.116 (b)(6).
[11] As presented to the committee in open session by Jason Malone on March 23, 2023.
[12] As presented to the committee in open session by Jason Malone on March 23, 2023.

of the Human Subjects Division at UW told the committee in open session that the university does not currently receive many claims.[13]

In a qualitative study of factors to facilitate research with pregnant women, a respondent from UW noted that "UW Medical Center has fewer research-related lawsuits and tort claims than do comparable institutions" (Mastroianni et al., 2020). This style of a compensation fund is used in other academic institutions but is typically more modest and provides limited coverage for those injured during research projects or clinical trials (Henry et al., 2015). With self-indemnity funds, the claim-filing process can be simple and provide easy and accessible coverage, but this is only possible when the fund is implemented correctly. In addition, the background of the funding of self-indemnity compensation schemes is also sometimes unknown and may lead to concerns over where the money is coming from to support the fund (e.g., donations).

In the clinical setting, evidence from the study of medical errors and medical malpractice suggests that compensation for harm may be an effective solution to mitigate liability for institutions and their investigators. A model that provided compensation, along with disclosure of a medical error, implemented within the University of Michigan Health System was associated with fewer lawsuits, shorter durations between claims and claim resolutions, and decreased institutional costs for liability payments (Kachalia et al., 2010). A similar program of compensation and disclosure at the Veterans Affairs Medical Center in Lexington, Kentucky, was found to be an effective solution to limiting costs related to liability payments (Kraman and Hamm, 1999). An analysis of compensation and disclosure programs found that an offer of compensation did not influence harmed individuals' interest in seeking legal advice, though the study did not evaluate whether harmed individuals proceeded to file a claim (Murtagh et al., 2012).

Agency-Affiliated Compensation Systems

Programs affiliated with federal government agencies include compensation systems covered by government institutions such as the Department of Defense (DoD) Clinical Investigation Program (CIP) or the Department of Veterans Affairs (VA) Office of Research and Development. The CIP program provides compensation for research-related injuries for all DoD-sponsored research. The VA Office of Research and Development provides compensation for research injuries for research approved by a VA IRB and conducted under VA supervision (Henry et al., 2015). These programs' injury claims are submitted to their specific

[13] As presented to the committee in open session by Jason Malone on March 23, 2023.

research offices, and then funding is adjudicated by the specific offices. For example, the CIP accepts claims and then assists the injured person to the correct facility for care. Most, if not all, agency-affiliated programs are funded by Congress, but the amount of funding for injury compensation is determined by the agencies themselves. Although these systems limit care to specific medical facilities, it provides some mitigation of liability for investigators and institutions that are covered by these policies.

Regulatory Guidance

There is no federal regulatory requirement that pregnant or lactating women be included in clinical trials; however, there is also no blanket prohibition against their inclusion. As discussed in Chapters 2 and 3, HHS regulatory requirements related to the inclusion of pregnant women in research are found in 45 CFR 46, Subpart B, "Additional Safeguards for Pregnant Women, Human Fetuses, and Neonates Involved in Research." Subpart B, as it is commonly known, includes directives regarding acceptable levels of research-related risk in research with pregnant women (Subpart B does not contain language on the inclusion of lactating women). In practice, however, the precise meaning and applications of the regulatory terminology around research-related risk, as well as its relationship to the prospect of research-related benefit, are subject to different interpretations by IRBs as well as investigators. The ambiguity and resulting uncertainty related to risk assessment have contributed to the exclusion of pregnant women from clinical trials (Krubiner et al., 2016; Mastroianni et al., 2017; ORWH et al., 2010; van der Zande et al., 2017).

Risk assessment is essential to the regulatory oversight and ethical conduct of clinical research, with implications for the permissibility of research as well as informed consent. Debates and variations in application of regulatory definitions of risk, particularly *minimal risk*, are not exclusive to research in pregnancy (e.g., Kopelman, 2004; Resnik, 2005). Minimal risk is defined in HHS regulations to mean

> the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.[14]

The regulations do not specify, for example, whether the daily life risk threshold is determined in reference to a healthy research participant,

[14] *Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,* 45 CFR 46.102(i) (2018i) (i).

a patient participant, or a healthy person. The regulations also can be interpreted to suggest that cumulative risk over many days is not relevant to decision making. Even where there is agreement on a standard, risk perception and characterization vary among individuals and stakeholders, leading to inconsistencies in application.

Those same debates and ambiguities become more complex in the context of pregnancy studies because they hinge on additional considerations of fetal risk. Specifically, Subpart B provides that a study that proposes no "prospect of direct benefit" to the pregnant woman or fetus can be performed if fetal risk is assessed to be "not greater than minimal." A study that proposes a prospect of direct benefit to the pregnant woman, the fetus, or both can go above the minimal risk threshold.[15] National-level approval by HHS is required for research that does not fit those requirements, although reportedly none has been sought (Saenz et al., 2017). Should an assessment of fetal risk take into consideration that the fetus of a pregnant woman with a medical condition may already be at elevated risk compared to the fetus of a healthy pregnant woman? Should the "daily life" risk standard account for whether a pregnant woman, and by extension her fetus, live in an unhealthy or dangerous environment, relative to other participants? Notably any such determinations would be inherently subjective.

The definitions of both *risk* and *benefit* are subject to variable interpretations, and little regulatory guidance exists, particularly for *minimal risk* (Blehar et al., 2013; Mastroianni et al., 2017; NVAC, 2017). In practice, this lack of clarity often results in conservative interpretations by decision makers that discourage conducting research with pregnant women (Mastroianni et al., 2017). IRBs do not have sufficiently clear guidance to evaluate appropriate study designs and safeguards for including pregnant women in clinical research that would permit their inclusion (Krubiner et al., 2016; Strong, 2011; White et al., 2021).

As more research with pregnant women is conducted, IRBs would benefit from assistance interpreting Subpart B from the HHS Office for Human Research Protections (OHRP). As discussed in Chapter 3, OHRP can help IRBs provide feedback on research protocols involving pregnant and lactating women and minimize harm to research participants by providing IRBs with clear guidance on safely conducting research in those populations. Further, guidance from OHRP on interpreting Subpart B can help to mitigate liability for regulatory-compliant institutions and their IRBs, in the same way that FDA guidance, discussed above, can mitigate liability for regulatory-compliant sponsors.

[15] *Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research*, 45 CFR 46.204.

MITIGATING LIABILITY FOR SPONSORS, RESEARCH INSTITUTIONS, AND INVESTIGATORS

Although there are mitigation strategies that differentially mitigate liability for industry sponsors, investigators, and institutions, some new and existing programs mitigate liability for all these stakeholders. Some of these concepts, such as clinical trial insurance, are currently in use by many stakeholders conducting clinical research but could be expanded to provide coverage for research involving pregnant and lactating women. Other strategies, such as a no-fault system for research-related injuries for pregnant and lactating women and tort reform, do not currently exist but could be created to mitigate liability for research stakeholders.

Clinical Trial Insurance

Clinical trials insurance covers the costs of compensation and legal fees if a participant suffers an injury or harm as a direct result of taking part in a clinical trial. It can be an essential tool in helping sponsors and others involved in the conduct of clinical trials protect their reputation, assets, and future research endeavors from potential liability and losses that may result from clinical trials. Such insurance may also help gain trust and confidence from the participants, regulators, investors, and other partners involved in clinical trials. Most policy holders are manufacturer–sponsors of clinical trials, but universities and other research institutions can also purchase insurance.[16] However, many large sponsors of clinical research often self-insure up to a certain amount and purchase reinsurance for large trials with potentially large liabilities. Most insurance policies extend beyond the sponsor to protecting other entities in the trial, such as IRBs, investigators (assuming protocols are followed), and contract research organizations.[17]

Although most payments from insurance come from a claim being filed and either settled or through the finding of fault in the tort system, most insurance policies provide some limited coverage for medical expenses if a participant is injured during a clinical trial.[18] In the event that an injury or illness occurs as the result of participation in the trial, including exposure to the treatment under study, the insurance policy covers the medical expenses up to a sublimit for any subject who is treated in a medical facility, called "med pay" (Dyson, 2023). The med pay system is usually a no-fault system, but the sublimit for expenses is usually fairly low.

[16] As presented to the committee in open session by Jason Malone on March 23, 2023.
[17] As presented to the committee in open session by Jason Malone on March 23, 2023.
[18] As presented to the committee in open session by Jason Malone on March 23, 2023.

Clinical trial insurance may mitigate liability for institutions and investigators by providing even modest compensation for research-related injuries and providing liability coverage should claims arise. However, institutions may be hesitant to purchase these plans because of their cost. If investigators were able to use federal grant funds to purchase clinical trial insurance, this would provide insurance for the investigator and their institution should any claims arise, therefore mitigating liability for the institutions and investigators. NIH currently covers clinical trial insurance as an allowable expense when clinical research sites are in countries that require clinical trial insurance (Henry et al., 2015). This policy could be extended to U.S. trial sites, allowing more investigators to purchase clinical trial insurance.

Obtaining trial insurance for research that includes pregnant women may be more difficult than for research that does not include pregnant women because of the uncertainty or potential severity of the risks involved (Manningham-Buller and Brocklehurst, 2022; Mastroianni et al., 2017). For example, the sponsors of an Ebola treatment trial were unable to get insurance coverage if they included pregnant women, despite strong recommendations from the World Health Organization that this population be included (Gomes et al., 2017). Taking steps to mitigate risk, many of which overlap with liability mitigation strategies, may help insurance underwriters feel more comfortable underwriting for research involving pregnant and lactating women and may result in better terms and conditions from the insurers. Because most trials exclude pregnant and lactating women before attempting to obtain insurance, challenges with obtaining insurance have so far not been as prominent an obstacle as other factors (NASEM, 2023).

Current federal regulations do not require researchers, institutions, or sponsors to provide medical care or compensation to those who are injured during clinical trials, and this has caused most academic institutions and government agencies to opt out of providing a compensation system (Henry et al., 2015). A study done in 2014 found "More than half of the U.S. research institutions surveyed do not offer free medical care or other compensation for research-related injuries," with less than 5 percent offering an "unconditional compensation" for harmful effects or injuries that resulted from the experimental intervention (Henry et al., 2015). While there was an increase in the number of institutions providing coverage from 2000 to 2015, the overall drive to develop a compensation system is unlikely to change without government pressure (Resnik et al., 2014).

No-Fault Administrative Compensation Systems

No-fault compensation systems include the National Vaccine Injury Compensation Program (VICP), described in detail in Box 4-1, and the

BOX 4-1
National Vaccine Injury Compensation Fund

The National Vaccine Injury Compensation Program (VICP) was created by the National Childhood Vaccine Injury Act of 1986 (HRSA, 2023c) after several lawsuits against vaccine manufacturers and health care providers threatened the risk of vaccine shortages and reduced vaccination rates (HRSA, 2023c). The program officially began accepting petitions in 1988, and even now, petitioners can receive compensation through a settlement even if a finding of harm from a covered vaccine is not made (HHS, 2019). There are two types of cases filed with the VICP: table injury cases and "non-table" or causation and fact cases. Table injury cases involve vaccines listed in the Vaccine Injury Table and make up most cases. All claims must meet the table's injury criteria and symptom onset to qualify for compensation. Those that file table cases are typically fast-tracked to the damages and compensation stage (Gentry, 2023). Non-table or causation and fact cases typically proceed as a standard litigation case, but it does not require the individual to provide proof of fault. While not required, most cases must provide sound and reliable scientific or medical explanations for the causation of injuries (Gentry, 2023).

Claims, Adjudication, and Funding

All petitions must be filed within 3 years after the first symptom of the alleged vaccine injury or within 2 years of the death and 4 years after the first symptom of the suspected vaccine injury that resulted in death (HHS, 2019). The VICP is funded by the Vaccine Injury Compensation Trust Fund from a $0.75 tax on vaccines recommended by the Centers for Disease Control and Prevention (CDC) for routine administration (HRSA, 2023a; Sands Anderson Vaccine Injury Legal Team, n.d.).

Challenges

The VICP suffers from limited staff, which is leading to a severe backlog of claims. When the program was first established, claims were expected to be resolved in less than a year. However, the Government Accountability Office (GAO) reports on the VICP have shown that claims take much longer (GAO, 1999, 2014). In a report that looked at petitions filed between 1999 and 2014, GAO found that the average time for adjudication took 5.5 years, while over half of petitions remained pending for over 6 years. This means that it takes longer to process claims through the VICP than through the tort system, which has an average adjudication time of just over 2 years (Engstrom, 2015). Another weakness of the VICP is the amount of funding provided to those affected. Pain and suffering compensation is capped at $250,000, which can pose issues if a pediatric patient experiences life-long consequences from a vaccine. Additionally, the program originally intended to have 50 percent of plaintiffs receive full pain and suffering payouts and the remaining 50 percent receive half of the maximum payout. According to Gentry (2023), it is exceedingly rare for an individual to receive a total pain and suffering payout.

Countermeasure Injury Compensation Program (CICP). The CICP was established in 2005 by passage of the Public Readiness and Emergency Preparedness Act.[19] In the event of a public health emergency or security dangers that threaten the United States, the government will support the development of countermeasures, and these can be in the form of vaccines, medications, medical devices, diagnostic test kits, or other items used to diagnose, prevent, or treat the emergency event (HRSA, 2023b). The CICP compensates for severe injuries or deaths that occur from the administration or use of a specific countermeasure (HRSA, 2023b). Some previously covered public health threats were COVID-19, Ebola, pandemic influenza A, smallpox, and anthrax (HRSA, 2023b). One important factor with the CICP is that liability protection is only enacted when a public health emergency declaration is made, it is only provided as a last resort for those seeking compensation, and the available funds are adjusted based on the type and severity of the emergency (HRSA, 2023b). No-fault systems have been particularly useful for granting compensation to injured participants as a finding of negligence is not necessary to receive compensation (Weiler, 1993).

Allowing research participants to choose an alternative to the tort system—such as a national system of no-fault compensation for injuries related to research involving pregnant and lactating participants—could achieve several aims. First, it would increase the likelihood that pregnant and lactating participants and their offspring or surviving kin would receive some financial recompense for harms that were probably caused by their participation in the research (Mariner, 1994). Second, such a system would redirect some—but not necessarily all—claims of harm away from the courts and into the no-fault system, which, by definition, does not assign blame to, or impose liability on, the individuals or institutions that sponsored or conducted the research, which means that the harms to reputation and morale caused by a finding of fault would be absent. Third, a no-fault compensation program for research-related injuries could diminish the fear those conducting the research have of large and unpredictable jury damage awards; payments by the research sponsors to fund the no-fault system would be more predictable and probably much smaller.

However, there are limitations to what a no-fault compensation program can accomplish. First, the amount of financial compensation through a no-fault system tends to be less than what could be awarded through the tort system (Engstrom, 2011). In addition, unlike the tort system, some no-fault compensation systems lack the element of deterrence. Whereas the tort system incentivizes sponsors, research institutions, and investigators

[19] *Public Readiness and Emergency Preparedness Act*, Public Law 109-148, 109th Cong., (December 30, 2005).

to optimize quality and minimize harm, no-fault compensation systems, depending on their design, may weaken or eliminate that incentive.

Since the evidence outlined in Chapter 2 points to limited liability for research with pregnant women and virtually no liability for research involving lactating women and there is not a national no-fault compensation program for clinical research generally, the most compelling argument for a no fault-compensation program for research involving pregnant and lactating women is that it is a better mode for compensation for research-related injuries, rather than a way to mitigate liability. While the committee supports compensating pregnant and lactating women and their offspring who are harmed when contributing to the societal benefit of clinical research, it has struggled to find reasons to create a national no-fault compensation program *solely* for pregnant and lactating research participants and their offspring. As many others have advocated (HEW, 1977; Mariner, 1994; Research, 1982), the committee favors a national no-fault compensation program for *all* clinical research participants, including pregnant and lactating women, but it is beyond this committee's charge to recommend such an all-encompassing system.

Although the committee is not recommending a national no-fault compensation program, some of the practical considerations for implementation of such are worth noting. There are numerous practical challenges to implementing a no-fault compensation program for research including pregnant and lactating women, particularly in regard to their offspring. A special challenge involves separating compensable research-related injuries from cases in which fetal demise or a child's congenital condition is unrelated to research participation (Mariner, 1994).

Discerning whether a child's injuries arose *from* or merely *during* parental participation in clinical research during pregnancy or lactation could be difficult or impossible because of the following reasons:

- Normal conception, gestation, and birth produces a wide range of congenital abnormalities or poor outcomes at baseline in offspring, including many that only become apparent later in childhood, but the occurrence of which led some parents to search for a singular cause to blame.
- The manifestation of injuries that affect prenatal development may be separated in time from exposure to the drug in the clinical trial.
- Rather than a defined set of adverse consequences (as is, for example, the case with childhood vaccinations, for which a federal compensation program exists) the wide variety of medical products in question would create a much larger list of conditions in children, some of which might be very rare, which could lead to prolonged and complex investigations into causation and in some cases a

child who suffered an injury in utero because of an investigational product would (unfairly) not be compensated by the system. The latter problem could be addressed by lowering the standard of proof of causation in the no-fault system (Mariner, 1994).

Although issues of causation are a challenge in the tort system as well, the tort system is set up to litigate individual cases to establish causation. To establish causation for individual cases on a national scale would drastically slow down payments in a national compensation program, leading to many of the same issues seen in the tort system. In fact, as covered in Box 4-1, this is what has happened with the VICP, leading to slower payments for claims than the tort system (Engstrom, 2015).

Tort Reform

Given the problems with the tort system and the potentially large awards that may result from the system, some have suggested tort reforms as a potential solution to mitigate liability (PRGLAC Task Force, 2020). Tort reform involves any attempt by lawmakers to make it more difficult for plaintiffs to file lawsuits or limit the amount of compensation a plaintiff may recover when filing a lawsuit. However, the tort system is already a difficult-to-navigate and inequitable system for some plaintiffs who have a meritorious claim (Franklin, 1967; Lytton et al., 2011; Mello, 2023).

There is a lot of imprecision in whom is awarded money through the system. Unfortunately, not everyone with a meritorious claim is awarded compensation, and inequities exist among claimants with similar injuries (Lytton et al., 2011). This is partially because the tort system can prove inaccessible to injured parties, leading to only major cases being brought because of the expense of bringing a lower severity case. There is also an equity problem with the tort system, as the lower a person's income, the lower the economic damages awarded (Paez and Liscow, 2022). If an attorney is working on a contingent fee, then lower damages awards mean a less attractive plaintiff for attorneys (Mello, 2023). In a survey of attorneys, over half of the attorneys were not willing to accept a case unless the expected damages were at least $250,000, even if they were almost certain to win the case (Sheperd, 2014). In cases with a less certain outcome, most attorneys required a minimum of $500,000 in damages to accept the case.

Therefore, the committee considered, but does not recommend, a mitigation strategy that places a cap on liability for investigators conducting research on therapeutics used during pregnancy and lactation (PRGLAC Task Force, 2020). There is some evidence that such tort reforms

do reduce levels of malpractice litigation, and they certainly reduce the amounts of damage awards (Yu, 2017). However, there is also evidence that the decrease in litigation caused by such reforms does not reduce provider anxiety about liability. At the same time, those reforms increased the likelihood of undercompensation for research-related injuries (DeVito and Jurs, 2014) and have a disproportionate effect on awards for those with the most serious injuries, as only the most seriously injured will have noneconomic damages that meet the limits set by the caps (Hubbard, 2020).[20] Tort reforms are also arguably more likely to disproportionately disadvantage women, children, and the elderly, who are more likely than men to have a greater proportion of their total damages come from noneconomic loss, such as emotional distress and grief, altered sense of self, impaired relationships, and more. Wages lost and health care expenses, which are more likely to be awarded to men of working age, have largely not been included in conversations around tort reform (Finley, 2004). As noted by one law professor, "by limiting noneconomic damages relative to economic damages, states may disproportionately reduce damage payments to women" (Sheperd, 2008). Finally, there is also some evidence that there is an increase in adverse patient safety events following adoption of damage caps (Zabinski and Black, 2022), which suggests that reform may undermine one of the key goals of the tort system: to deter negligent conduct.

MITIGATING CRIMINAL AND CIVIL LIABILITY FOR PREGNANT RESEARCH PARTICIPANTS

Complicated privacy concerns have long been an issue for research involving pregnant women, often stemming from a state's stated interest in minimizing any risk to fetuses while in utero. For example, an IRB at the University of South Dakota encountered such privacy issues when the IRB was presented with a protocol for a five-state study of fetal alcohol syndrome that involved identifying and monitoring women who drink during pregnancy. South Dakota law, however, requires officials to report behavior the state defines as abusive toward a fetus, including drinking alcohol. At that time, investigators were unable to offer research participants a certificate of confidentiality or other privacy protection because of state law. As a result, women who volunteered for the study were at risk of being reported to state officials and potentially facing legal repercussions because of their substance use while pregnant. Ultimately, the governor's office wanted the study to proceed because its objectives

[20] *N. Broward Hosp. Dist. V. Kalitan*, 219 So. 3d 49 (Fla. 2017).

involved a positive intervention—helping pregnant women with drinking problems with educational interventions intended to help them maintain sobriety. Under the state's decision, the women would still be reported to the state, but the state would take no action against participants of the study (*IRB Advisor*, 2003).

As covered in Chapter 2, the U.S. Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* overturned its previous rulings that the U.S. Constitution protected the right to an abortion. Post-*Dobbs*, the breadth of privacy issues may increase as states propose and enact new laws aimed at preventing abortion, protecting fetal life, and regulating the bodies and choices of pregnant women. The current legal environment, including its instability, underscores the importance of protecting the confidentiality of all information about trial participants' pregnancies and use of abortion services (Appendix E).[21]

The post-*Dobbs* climate may affect how researchers record pregnancies among subjects and whether and how that information is protected from disclosure. In many clinical trials involving nonpregnant subjects, initial and periodic pregnancy tests are a standard part of trial protocol. These tests are deemed necessary when a trial's protocol requires exclusion of pregnant women, yet they may also detect early pregnancies that would have otherwise gone unnoticed because of high rates of first trimester miscarriages. A positive pregnancy test during the course of a trial is typically considered a "reportable event," so participants must be willing to report their pregnancies and feel secure doing so, particularly if they are considering an abortion. According to Aoife Brennan, chief executive officer of Synlogic:

> [*Dobbs*] is forcing people involved in clinical research to rethink something as simple as pregnancy tests, which had once been taken for granted, and plan for the possibility that research sponsors and study sites will be required to share pregnancy and outcome data with state officials. (Skerret, 2022)

According to a recent analysis on potential implications of *Dobbs*, "the simple fact that a research participant is not pregnant nor has given birth, but a test indicates that they were pregnant during research, could put them at risk of legal action" (Sugarman et al., 2023).

In most if not all cases, the information reported to states maintains the patient's confidentiality and does not provide their name or other personally identifiable information. However, where a state has banned or severely restricted abortion, state officials may seek such identifiable

[21] Appendix E can be viewed online at https://nap.nationalacademies.org/catalog/27595.

information in pursuit of criminal charges, which may involve participants, investigators, or the investigators' institutions.

Overall, the risk of criminal and civil liability will likely increase post-*Dobbs* for participants, investigators, and their institutions involved in research with pregnant women. This will be particularly true in states with fetal personhood laws, fetal homicide laws, or where state child abuse statutes have been interpreted to encompass risky behavior by a pregnant woman that may affect her fetus (Appendix C).[22] Researchers have also posited that:

> It is easy to imagine that in a legal context where fetal harm is more likely to result in criminal penalties, especially among women of color . . . the research community might conclude that a study with pregnant persons is too risky to justify—to funders, to research oversight boards, or to pregnant persons themselves. (Waggoner and Lyerly, 2022)

The potential for criminal and civil liability depends on how far states are willing to push their antiabortion and fetal protection laws. While some states may limit their actions to research explicitly studying drugs intended to induce an abortion, others could go further, seeking to impose liability on those involved in clinical research that may harm a fetus or result in fetal death. The liability could stem from a state's abortion laws, fetal personhood laws, child endangerment and abuse laws, or other criminal laws.

Certificates of confidentiality (CoCs) provide an important tool to protect research participants against privacy breaches. CoCs were created to provide participants with greater certainty that their privacy concerns are addressed, so participants who have such concerns would be willing to participate in research (UVA, n.d.). CoCs likely provide privacy protections in many of the contexts involving pregnant women in clinical research. However, many research institutions, IRBs, and investigators do not understand the full statutory power of CoCs and therefore discount the privacy protections that they afford. These stakeholders may also misunderstand the complexities of the privacy protections that they afford and may unwittingly undermine the privacy protections provided.

The CoC is a federal statutory device that protects identifiable, sensitive information collected during "biomedical, behavioral, clinical, or other research" from compelled disclosure (UVA, 2019). Specifically, if a law enforcement officer, prosecutor, legislator, civil litigant, or other party seeks to compel information about a research participant through a subpoena or warrant, a CoC allows the researcher to refuse the disclosure and bars the use of that information as evidence. By protecting researchers

[22] Appendix C can be viewed online at https://nap.nationalacademies.org/catalog/27595.

and institutions from being compelled to disclose information that would identify research subjects, a CoC can help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

A recent analysis demonstrates that legal challenges to the privacy protections afforded by CoCs will likely fail, with the possible exception of challenges based on constitutional criminal defense rights (Ram et al., 2022). CoCs are therefore a remarkably strong tool for protecting privacy rights, and there is reason to believe that they can be relied upon to protect pregnant participants' privacy. In research contexts, CoCs add a layer of protection that may not be available under the Health Insurance Portability and Protection Act (HIPAA). HIPAA *allows* a covered entity to refuse a subpoena or a warrant; HIPPA does not *compel* a covered entity to do so. In contrast, recent amendments to the law governing CoCs prohibit researchers from disclosing "any identifiable, sensitive information about [an] individual . . . that was created or compiled for purposes of the research."[23] Moreover, although the statute that authorizes CoCs does permit disclosures "as required by federal, state, or local laws" (e.g., public health reporting requirements),[24] researchers may not do so unless they have obtained the consent of the participant.[25] Nonetheless, researchers in states where their institutions may be subject to political or other pressures to comply with state- or court-mandated demands for information should also recognize that their efforts to protect the private information of their participants may be hampered by institutional pressures.

Legally, the issuance of CoCs is automatic for all NIH-funded research that collects or uses identifiable, sensitive information; research funded by agencies other than NIH may be granted a CoC automatically through the funding agency if the agency issues them. If the research is funded by an agency that does not issue CoCs, investigators may apply to NIH for a CoC. Researchers not engaged in federally funded research are eligible to apply for a CoC at NIH. As a result, large volumes of research data are now covered by CoCs and therefore may be beyond the reach of state and federal law enforcement, legislative bodies, and other authorities. CoCs provide some reassurance to participants that their data are safe and protected from disclosure or use in legal proceedings. As a result, participants may feel more comfortable about participating in research.

[23] *Research and investigations generally,* 42 U.S.C. §241(d)(1)(D).
[24] *Research and investigations generally,* 42 U.S.C. §241(d)(1)(C)(i).
[25] *Research and investigations generally,* 42 U.S.C. §241(d)(1)(C)(iii).

CONCLUSIONS

Conclusion 4-1: Regulatory ambiguity in Subpart B and resulting uncertainty related to risk assessment have contributed to the exclusion of pregnant women from clinical trials.

Conclusion 4-2: Close adherence to federal guidance and regulations relevant to clinical research may provide evidence that may mitigate liability for sponsors, institutions, and investigators.

Conclusion 4-3: No-fault compensation programs for research-related injuries are a factor that may help mitigate liability for sponsors, institutions, and investigators. This mitigation strategy is not specific to research involving pregnant and lactating women; rather, it would mitigate liability for all human subjects research. A national no-fault compensation program would provide an important benefit to all clinical research participants.

Conclusion 4-4: Clinical trial insurance is a factor in mitigating the financial uncertainty associated with liability for institutions and their investigators by providing certain coverage for research-related injuries and insuring against potential liability claims. However, these insurance plans may be cost prohibitive for many institutions. Adding clinical trial insurance as an allowable expense for federal grants supporting research including pregnant and lactating women can help to offset some of these costs.

Conclusion 4-5: Certificates of confidentiality help protect the privacy of research participants, which can mitigate their exposure to liability arising out of state laws concerning fetal harm arising in the course of clinical research.

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5

Dissuasive and Persuasive Factors for the Inclusion of Pregnant and Lactating Women in Clinical Research

In response to its statement of task, the committee focused on exploring how the real and perceived risks of legal liability can be reduced in order to encourage the individuals and organizations that are involved in the development, testing, oversight, approval, and marketing of medications and vaccines to include pregnant and lactating women in clinical research. If a sponsor or other stakeholder considers conducting studies with pregnant and lactating women, it evaluates the reasons for and against doing the research, incorporating considerations related to uncertainties and assessments of legal liability exposure; potential reputational losses; and financial, technical, and practical considerations associated with the complexity of the trial, among others. For pharmaceutical companies in particular, factors that enter into the decision-making process include the state of the science concerning the disease or condition, pathway, and the investigational product; the unmet medical need; the cost and complexity of the laboratory, preclinical, and clinical research; when and whether the company will be able to recoup its costs; the competitive landscape; and regulatory requirements.[1] Companies may also weigh the decision to conduct research with pregnant and lactating women with whether data on safety and efficacy could be collected in animal models or through postmarketing studies, such as pregnancy registries.

If the considerations against doing the research outweigh those in favor of doing the research—for example, because of unpredictable

[1] As presented to the committee by Kirke Weaver in open session on June 16, 2023.

liability exposure, uncertain financial return, and ambiguity in regulatory requirements—the sponsor and others are likely to decide not to include pregnant and lactating women in research. Thus, decisions to pursue research involving pregnant and lactating women are influenced by perceptions of liability that are inextricably intertwined with other factors that have contributed to the exclusion of pregnant and lactating women from clinical research. For example, a decision about the appropriate selection of participants is only one step in the product's research and development process, and potential liability is only one factor—and not necessarily the decisive one—in deciding whether to conduct research with pregnant and lactating women. Importantly, changing one or more factors could offset and overcome potential liability concerns, and addressing interrelated factors together could affect how a stakeholder views liability in the decision to do research with pregnant and lactating women.

Because of the interconnected relationship between liability and other such factors, and because factors that enter into decisions to include pregnant and lactating women in research are sometimes termed *liabilities* even though they involve no legal risk, this chapter presents the committee's consideration of several factors that can affect liability assessments and contribute to stakeholder decision making concerning the inclusion of pregnant and lactating women in research.

FACTORS THAT DISSUADE SPONSORS AND INVESTIGATORS FROM INCLUDING PREGNANT AND LACTATING WOMEN IN RESEARCH

The factors that dissuade the various stakeholders in the development and use of medical products from including pregnant and lactating women in clinical research affect the entire pathway of medical product development, from preclinical studies to postapproval surveillance. This chapter explores these dissuasive factors, which include the following:

- Culture of exclusion
- Recruiting and enrolling patients
- Lack of expertise in research involving pregnant and lactating women
- Reputational risk
- Cost and complexity
- Lack of financial incentives

As noted above, these factors interact with the potential for legal liability; they also interact with one another and other factors that are perceived as potentially persuasive factors. For example, a lack of financial incentives to conduct a trial with pregnant and lactating women is worsened by the potentially high costs of conducting such a trial, including the

sponsor's coverage of potential liability. The financial considerations make it less likely that these trials will be conducted, thus contributing to the problem of a dearth of expertise in research involving pregnant and lactating women. Many of these factors overlap and affect one another; any mitigation strategies must take these relationships into account.

Culture of Exclusion

Pregnant and lactating women have historically been excluded from research; this is one of the most entrenched barriers to conducting research on pregnant and lactating women and has become a cultural mindset (Little and Wickremsinhe, 2017; Trahan et al., 2021; White et al., 2021). Gender bias has deep social roots that extend far beyond medicine, but there is no question that its effects are still felt in medicine. Women were systematically excluded from health professions in the nineteenth century, mirroring their exclusion in many other businesses and professions (Starr, 1982). This underrepresentation resulted in an underfunding of research related to women's health (Mirin, 2021).

By the mid-twentieth century, medical research became centered on the notion of the male norm (Cotton, 1990). This meant that between World War II and 1994, most clinical research focused on men (usually White men). Some of this point of view was sociological, an adoption of male perspective viewing the female physiology as the deviant (IOM, 1994). Some of this point of view was expedient; female sex presents a more complicated medical model. The physiological changes associated with the menstrual cycle add significant variation to testing a drug or other treatment. And females, at least until menopause (which is associated with its own hormonal variability), can become pregnant. Paradoxically, although female variation was a recognized challenge in research, it was generally assumed that women would respond similarly to men once drugs were on the market (IOM, 2001; Liu and Mager, 2016).

The thalidomide and diethylstibestrol (DES) experiences furthered the idea that women of childbearing age and pregnant women should be excluded from trials even though those events were not the result of clinical trials. In fact, it is likely that had clinical trials for thalidomide and DES applied modern study design, these trials would have significantly minimized the damage by revealing that thalidomide was teratogenic and that DES was ineffective for use in pregnancy (see Chapter 2).[2] Revelations of abuses in human research led to calls for additional protections, especially

[2] Although DES was also teratogenic and caused harm in the female offspring of those who took DES while pregnant, those harms likely would not have been uncovered by an appropriately conducted clinical trial because of the long-term follow-up that would be needed to identify the adverse event.

for vulnerable populations. Subsequently, the U.S. Food and Drug Administration (FDA) adopted guidance in 1997 that advised against including women of childbearing potential in Phase I and Phase II clinical studies (FDA, 1997). In excluding women with the potential to become pregnant, the focus was on the protection of not just an existing fetus, but on the protection of a potential fetus.

Only 2 years later, the Belmont Report recommended that the principle of justice guide the fair inclusion of research participants (HEW, 1979), and in 1994, an Institute of Medicine committee directly recommended that pregnant and lactating women not be excluded from clinical studies (IOM, 1994). However, the recommendations focused on pregnant and lactating women from the IOM report were largely not translated into law, policy, or practice. Instead, a culture of fetal protection surrounded the question of women's participation.

In the late 1980s, the National Institutes of Health (NIH) began to encourage the inclusion of women and minorities in clinical research. The NIH Revitalization Act of 1993 (Public Law 103-43) required the inclusion of women of childbearing age and minorities in federally funded clinical studies. However, as mentioned in Chapter 1, while there has been a growing recognition of the need to include pregnant and lactating women in clinical trials in recent years—such as through the Task Force on Research Specific to Pregnant Women and Lactating Women—the long-standing culture of an exclusion mindset persists, preventing the generation of needed evidence to support medical treatments for pregnant and lactating women.

This lack of evidence generation applies to both understanding the safety and efficacy of approved products in pregnant and lactating women, as well as a lack of development of medical products for conditions specific to pregnancy and lactation. For example, pregnant women were paradoxically excluded from the initial COVID-19 vaccine trials, despite evidence that pregnant women were at risk for more severe complications and at greater risk of death (Rubin, 2021), which also placed their fetuses at risk. The exclusion from trials, and the higher risk of severe outcomes from COVID-19 infection, made it challenging for patients and their providers to make informed decisions about vaccination (Minkoff and Ecker, 2021; Riley, 2021).

In addition to the historical precedent of exclusion, there are several cultural mindsets that contribute to the culture of exclusion: the "fetus-first" mentality, the precautionary principle, and an underappreciation of the benefits of inclusion. In the fetus-first mentality, the life and well-being of the fetus is prioritized over the life and well-being of the pregnant woman (Milne, 2020). With the 2023 Supreme Court decision in *Dobbs v. Jackson Women's Health Organization* holding that each state

may determine how to balance the rights of the fetus against the rights of the pregnant woman, some states have moved to adopt "fetal personhood" laws, in which a pregnant woman can be held criminally liable for the injury or death of the fetus (Carpenter, 2023). These laws could target pregnant women who take medications that have the potential to cause fetal harm, whether in the course of regular treatment or in a clinical trial (Carpenter, 2023). These laws—and the associated mentality—further the culture of exclusion, affect the behavior of health care providers, and impede research on women's health generally (Paltrow, 2022).

A second factor that contributes to the culture of exclusion is the precautionary principle and how it is often applied in the context of pregnant women. The precautionary principle, commonly associated with environmental hazards, reverses the burden of proof by requiring that an intervention or action be proven safe before it is implemented (Kukla, 2016). When applied to research in pregnant women, this principle is often understood to mean that pregnant women should be entirely excluded from clinical research because of the risk of fetal harm (Lyerly et al., 2008). This interpretation has been incorporated into both policy and practice, resulting in the routine and systematic exclusion of pregnant and lactating women from research (Kukla 2016). For example, Subpart B of the HHS regulations requires research involving pregnant women that does not confer either a direct benefit to the pregnant woman or the fetus to involve no more than "minimal risk."

Although the policy does allow for pregnant women to be enrolled in research that confers more than "minimal risk" if it offers the potential for direct clinical benefit to the pregnant woman or the fetus, in practice, many institutional review boards (IRBs) interpret this policy conservatively, resulting in the exclusion of pregnant women from clinical research, as discussed later in this chapter. However, the exclusion of pregnant and lactating women does not serve to eliminate risks of harm to this population; in fact, exclusion itself presents risks of harm owing to the lack of evidence on safe and effective treatments for pregnant and lactating women.

Much attention has been given to the potential harms of including pregnant and lactating women in research, but there has been less conversation and deliberation about the benefits of inclusion; this lack of appreciation for the benefits of inclusion is another factor that drives the culture of exclusion. Without fully appreciating the benefits of research for the health and well-being of pregnant and lactating women and their offspring, and without recognizing the interconnected nature of the health of pregnant and lactating women and their offspring or the harms to those populations from untreated or inadequately treated medical conditions

resulting from pregnant and lactating women's exclusion from research, decision-making stakeholders—including IRBs, research institutions, clinicians, and potential research participants—may view research as too risky an endeavor. Yet, pregnant women may choose, and indeed do choose, to enroll in clinical research for a variety of perceived benefits. These include close monitoring from research staff, early access to a new medical product, the potential for better outcomes for themselves and their fetuses, and the ability to help individuals who may be in similar situations as them in the future (Kenyon et al., 2006; Meshaka et al., 2017; Smyth et al., 2012).

Recruiting and Enrolling Participants

The reasons pregnant women participate in clinical trials are the same reasons that people generally participate in trials: aspirational benefits and altruism (van der Zande, 2018). Despite this, recruiting and enrolling participants in clinical research is challenging and many of the factors that may be challenging for enrollment in clinical trials can be heightened during pregnancy or while caring for a newborn or child. Pregnancy and early parenthood can be stressful—particularly if a medical issue arises—and being confronted with a decision about participation in a trial can further complicate an already stressful set of circumstances (Kenyon et al., 2006; Manningham-Buller and Brocklehurst, 2022). Clinicians—who often serve as the gatekeepers to clinical research—may be unaware of potential studies or unwilling to refer their patients to studies (Frew et al., 2014; van der Zande et al., 2016). If patients are aware of investigational studies, they are likely to have concerns about the safety of participation for themselves and their fetus or baby, as well as questions about possible benefits (NASEM, 2023; Rodger et al., 2003). Pregnant and lactating women often have a strong preference for their own provider and may be hesitant to join a study that requires them to visit a different provider (Frew et al., 2014).

Although not specific to pregnant or lactating participants, transportation, access to the study site, and related expenses can all be significant obstacles for participation, especially for lower-income patients (Frew et al., 2014; NASEM, 2023). Some patients, particularly those from historically marginalized groups, may distrust the research enterprise or the health care system, owing to past harms such as the U.S. Public Health Service Syphilis Study at Tuskegee and the unauthorized use of Henrietta Lacks HeLa cells, as well as current harms of not being believed, in addition to racism and bias experienced while receiving health care or trying to access health care (Frew et al., 2014; Le et al., 2022; NASEM, 2023; Russell et al., 2008). Lactating patients may be hesitant to participate in research because of concerns about disruption of breastfeeding, maintaining their

milk supply, cost constraints related to formula feeding and supplementation, and any potential effect on their babies' health (Zhao et al., 2018).

Furthermore, traditional pharmacokinetic studies to determine the exposure to a drug usually require serial blood draws over a period of 6–24 hours, which can be disruptive to pregnant and lactating women, particularly for those farther along in their pregnancy or who have multiple young children including the child or children they are breastfeeding (NASEM, 2023). These studies may also require pregnant participants to return to a study site multiple times throughout their pregnancy and postpartum to determine how physiological changes throughout pregnancy affect the pharmacokinetics of medications (Avram, 2020). Finally, pregnant and lactating women may have a job outside the home or caregiving responsibilities that they are unable or unwilling to disrupt in order to participate in a trial (Keitt, 2013; NASEM, 2023).

While beyond the scope of this committee, implementing evidence-based strategies for successfully recruiting participants may require enhanced support for investigators and pregnant and lactating women who wish to conduct or participate in clinical research. Evidence points to several factors that may positively influence pregnant women's decisions to participate in clinical studies, including ease of transportation and access to research sites, supportive attitudes from family and friends, and studies using community-based methods (Frew et al., 2014). At a minimum, clinical investigators must account for cultural considerations, particularly during the informed consent process, and respect the roles of family members, spiritual leaders, and other community leaders during the decision-making process.

Lack of Expertise in Research Including Pregnant and Lactating Women

There is an absence of relevant expertise among researchers, members of IRBs, institutional leaders, and other stakeholders in conducting clinical research with pregnant and lactating women. There are a number of factors that contribute to this absence of expertise. Because clinical trials have historically excluded pregnant and lactating women, researchers, members of IRBs, institutional leaders, and other stakeholders have generally been unable to gain the knowledge and experience necessary to champion and lead research in this area. Research during pregnancy, childbirth, and lactation in general is underfunded; despite high rates of maternal morbidity and mortality in the United States, funding for research in this area has historically been low (Longo and Jaffe, 2008; NIH, 2023d). As a consequence, there is a limited number of grant opportunities, training, and career development opportunities for researchers working in this area (Longo and Jaffe, 2008).

The limited research funding and opportunities for career advancement coupled with competing financial and clinical demands lead clinical investigators to choose other areas of focus, contributing to a shortage of a trained workforce with the expertise and professional knowledge required to conduct research in pregnant and lactating women (Sadovsky et al., 2018). Compounding the lack of advancement opportunities is the shortage of obstetricians and gynecologists and pediatricians who are trained in the various skills of clinical research (NASEM, 2023), including clinical pharmacology for Phase I studies and research design, and execution and evaluation for Phases II and III. In fact, some residents in obstetrics and gynecology report that research is not promoted during their training or is financially disincentivized (Oakley et al., 2013).

The lack of expertise among researchers both contributes to, and is exacerbated by, the lack of expertise among other stakeholders. For example, many IRB members lack training or guidance in assessing the risks and benefits of research with pregnant and lactating women (Lyerly et al., 2008; Saenz et al., 2017; van der Zande et al., 2016), and they may see few, if any, research proposals that include pregnant and lactating women. One study of IRB members across the United States found that over 67 percent of respondents reported infrequently encountering protocols that included pregnant women (White et al., 2021). As a consequence, they may be unable or unwilling even to consider approving such a proposal (Saenz et al., 2017). Denial of these proposals further erodes the opportunities for researchers to pursue work in this area.

Reputational Risks

Conducting research with pregnant and lactating women carries reputational risks for the companies that develop new medical products and the researchers and institutions that carry out the studies required for licensing. Given that injuries to fetuses and babies have particular emotional valence, these stakeholders may fear adverse consequences for their reputation if pregnant and lactating women or babies are harmed in the course of research, particularly if the research is perceived as exploitative or lacking safeguards. For example, researchers and their institutions have a desire to maintain a positive reputation for ethical research in order to attract future funding. Stakeholders may avoid including pregnant and lactating women in research on new medical products owing to fears of injuries and negative media attention such as that which accompanied the harm to pregnant women and their offspring associated with thalidomide, DES, and doxylamine/dicyclomine/pyridoxine (Bendectin) (Manningham-Buller and Brocklehurst, 2022).

Ironically, these high-profile cases involved products that had been licensed for use without being tested in pregnant women. Thalidomide was prescribed to pregnant individuals to treat nausea, but it was not approved in the United States for this indication owing to a lack of safety data. Later, thalidomide was found to cause severe congenital malformations, notably limb deformities.

Among other uses, DES was prescribed to treat pregnancy complications but was discontinued after a link was discovered between the use of DES and a higher prevalence of cancer in the offspring (see Box 2-1). In contrast, many lawsuits were filed against the company that manufactured Bendectin, which was approved to treat nausea and vomiting during pregnancy, claiming it caused congenital malformations. The cost to defend against these lawsuits exceeded the profit made from the drug (Green, 1996) even though research found no association with the drug and malformations (Willhite, 2005). Nonetheless, the company withdrew Bendectin from the market. Another company reintroduced a similar combination product in 2013.

Cost and Complexity

The clinical research community has historically resisted including women in research owing to concerns that factors such as hormonal differences, menstrual cycles, menopause, and pregnancy would make research more complex, time consuming, and costly (Keitt, 2013; Rothenberg, 1996). While there has been significant progress on the inclusion of women in general in clinical research in recent years, pregnant and lactating women are still routinely excluded in part because of the same concerns about complexity and cost (Rothenberg, 1996; van der Zande et al., 2016). Studying the safety and efficacy of a medical product in pregnant or lactating women most likely would require separate trials, rather than simply including pregnant and lactating women in a trial of the general adult population (van der Zande et al., 2016).

Separate trials are needed for pregnant and lactating women because study enrollment must be large enough to detect differences between treatment and nontreatment groups, meaning that the inclusion of a few pregnant and lactating women in a general trial may not produce sufficient information on the safety and efficacy of the product in these subpopulations. And developing medical products for conditions specific to pregnancy and lactation may require even larger trial populations to gain FDA approval. However, conducting these trials incur costs in addition to the initial costs of research.

Further, if pregnant and lactating women or other small subpopulations are included in clinical studies, the small numbers of patients may

lead to a false finding of a safety signal or a finding of lack of efficacy simply because the more subpopulations that get analyzed, the higher the chances of a spurious result. This finding could raise questions of the safety of the drug overall and delay approval or prevent approval of a medical product, which would delay or deny access to a potentially effective medical product for populations that could benefit from the product and hinder the sponsor's ability to recuperate its investment in the development of the product, as discussed in the section that follows. Further, a false finding could cause potential liability postmarketing if the product already has FDA approval.

Pregnancy is a complex biological process, and designing and conducting trials that are capable of detecting safety signals in this population of rare or delayed events may be more challenging; for example, a larger sample size may be required (van der Zande et al., 2016). Pharmacokinetics and pharmacodynamics may change during pregnancy, requiring careful dosing and monitoring (Coppola et al., 2022; Zajicek and Giacoia, 2007). Conducting a trial in this population may require additional infrastructure and training for investigators; for example, measuring outcomes related to pregnancy and the health of the newborn may require years of follow-up monitoring, which requires specific expertise to adequately design and run a long-term trial sufficiently powered to detect rare events, along with the associated personnel and financial resources needed (Dangel et al., 2022).

There are also additional costs and potential delays caused by the challenges of recruiting and enrolling these populations in clinical research, as discussed earlier in the chapter. There may be other needs in the research setting that add costs, such as child care, support for nursing participants, and the equipment necessary to monitor the health of both the adult participant and the fetus or baby. Despite the potential increased costs, it should be noted that for research that is funded by NIH, NIH guidelines on inclusion of women and minorities specifically state that cost is not an acceptable reason for excluding a population from a trial, although these guidelines do not apply to industry-sponsored research or other research not funded by NIH (NIH, 2017). Current NIH R01 grant caps may be too low to support the conduct of adequately powered clinical studies with pregnant women or the follow-up of offspring for prolonged periods.

Lack of Financial Incentives

There are few financial incentives for industry researchers to include pregnant and lactating women in clinical research. The market for drugs specifically targeted at pregnancy-related conditions is small, and drugs

for concurrent conditions (e.g., diabetes, hypertension) are already commonly prescribed to pregnant women despite the lack of information about appropriate dosing and evidence about clinical outcomes in this population (Mastroianni et al., 2017). When a drug is approved for use in the adult population, approval extends to pregnant and lactating women unless explicitly stated otherwise on the product label. Unlike the pediatric market, where additional studies can allow a sponsor to add these patients to the label of a drug previously only licensed for use in adult patients, additional testing is not needed to allow these drugs to be marketed to pregnant and lactating women.

One potential financial benefit for conducting studies with pregnant and lactating women are the advertising privileges that would come with conducting safety and efficacy studies in pregnant and lactating women. This may confer some financial benefit for manufacturers, as they could specifically market the product to these populations, whereas other generics without this information would not have these capabilities. However, the market for a particular product may be too small to be much of a financial incentive for sponsors. Thus, a commercial sponsor can expect little to no return from funding clinical research with pregnant and lactating women. Given the competing demands on limited clinical research budgets, it is not surprising that research companies would not prioritize research with pregnant and lactating women over other studies with the prospect of greater financial returns.

Including pregnant and lactating women in clinical trials may add cost, time, and complexity to the trial, while offering few regulatory or marketing advantages (Mastroianni et al., 2017; van der Zande et al., 2016). Indeed, new risks identified through such inclusion could negatively affect the perceived risk–benefit profile and therefore sales of the drug for the broader population. Further, the inclusion of pregnant and lactating women in a trial opens up the possibility of financial risks if the sponsor must provide compensation for harm suffered by the pregnant and lactating women, the fetus, or baby. Of course, liability may arise if an approved product causes harm in clinical use, but the risk of liability generally rests with the health care provider who prescribed the medication, while a manufacturer who has provided the provider with information about the medication that is accurate and adequate for licensing is protected under the "learned intermediary" defense, as discussed in Chapter 2 (Mastroianni et al., 2017). Even when research is conducted by academic institutions, rather than private industry, the financial calculus for including pregnant and lactating women is similar. To attract industry sponsors for public–private partnerships, academic institutions have a strong incentive to conduct research that aligns with the financial interests of private industry (Mastroianni et al., 2017).

FACTORS THAT INCENTIVIZE THE INCLUSION OF PREGNANT AND LACTATING WOMEN

The effectiveness of various policy strategies for mitigating risk and encouraging research in pregnant and lactating women will differ depending on where a drug is on the product development and approval pathway. From the standpoint of financial incentives and study funding, it is most helpful to focus on three stages of the pathway for medical products: preapproval; on-market, on-patent (postapproval before generic entry); and on-market, off-patent (postapproval after generic entry). The sections that follow cover each of these stages in reverse order to first focus attention on the current backlog of medical products on the market for which no or little data from human trials exist to inform their use in pregnancy or lactation. However, it is crucial that policies to promote clinical research target each of these three stages in a product's life cycle to prevent the perpetuation of the current backlog and so pregnant and lactating women can have access to new therapeutics in a timely manner.

On-Market, Off-Patent Products

The majority of medications that pregnant women take are off-patent (Palmsten et al., 2015). Drug companies generally rely on the time a drug is on-patent to recoup research costs and make a profit (Grabowski et al., 2015). Once a drug's patent and exclusivity periods have expired and generics have entered the market, companies generally have no financial incentive to conduct additional research, including with respect to use in pregnant and lactating women. Therefore, funding sources beyond pharmaceutical companies are likely needed to conduct research with pregnant and lactating women for products that are off-patent.

Research Investment

As outlined in Chapter 1, conducting research with pregnant and lactating women provides societal value by reducing health inequities in the United States. Given the lack of financial incentives for medical product manufacturers to conduct research after their patent has expired and the societal value this research provides, research for off-patent products in pregnant and lactating women is ripe for government support. As the nation's largest funder of clinical research, NIH is the most appropriate source of investment in clinical research in pregnant and lactating women for on-market, off-patent products. NIH has already adopted multiple initiatives to improve clinical research in pregnant and lactating women (Box 5-1). Further, there are precedents for the government funding clinical research through NIH to study off-patent medical products. NIH funding

BOX 5-1
NIH Initiatives in Pregnancy and Lactation Research

NIH hosts or supports a number of efforts directed at expanding knowledge about the use of medical products during pregnancy or breastfeeding. Many of these efforts are under the umbrella of NIH's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). NIH programs and initiatives include the following:

- The International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network is a collaboration of investigators and institutions that evaluate treatments and interventions for HIV in pregnant women, infants, children, and adolescents (NIH, 2023e).
- The Global Network for Women's and Children's Health Research supports and conducts clinical trials in resource-limited countries, with the aim of improving maternal and child health while building local research capacity (NIH, 2023d).
- The NICHD Data and Specimen Hub (DASH) is a centralized resource that allows researchers to share and access deidentified data from studies funded by NICHD and serves as a portal for requesting biospecimens from selected DASH studies (NIH, n.d.a).
- The Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB) supports research and research training on the development and use of safe and effective therapeutics for children and pregnant and lactating women (NIH, 2023h).
- The Maternal–Fetal Medicine Units Network (MFMU) is a collaboration of clinical centers that conduct research in maternal–fetal medicine and obstetrics. The network's research studies are focused on addressing maternal, fetal, and infant morbidity related to preterm birth, fetal growth abnormalities, and maternal complications, and to provide the rationale for evidence-based, cost-effective obstetric practice (NIH, 2023g).
- The Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub serves as a national resource for expertise in maternal and pediatric therapeutics to conduct and foster therapeutics-focused research in obstetrics, lactation, and pediatrics, while enhancing inclusion of people with disabilities. The MPRINT Hub webinar series is focused on educating the biomedical community on research approaches that can be applied to pregnant and lactating women, as well as pediatric populations (NIH, 2023f).
- The Implementing a Maternal health and Pregnancy Outcomes Vision for Everyone (IMPROVE) initiative supports research to reduce maternal deaths and improve health for women before, during, and after delivery. As part of the initiative, NIH launched and funded the Maternal Health Research Centers of Excellence (NIH, n.d.b).
- The Breastmilk Ecology: Genesis of Infant Nutrition (BEGIN) Project studies human milk and its effect on infant and maternal health (NIH, 2023b).

These initiatives form a portion of the funding NIH provides to conduct research in areas related to pregnancy, lactation, and the health of pregnant and lactating

BOX 5-1 Continued

women and their children. Funding data from 2022 (NIH, 2023c) show that NIH provided funds in the following amounts:

- Pregnancy: $635 million
- Breastfeeding: $141 million
- Maternal health: $558 million
- Maternal morbidity and mortality: $346 million
- Perinatal period: $909 million
- Preterm, low birth weight, and health of the newborn: $435 million

Although this sounds like a substantial amount, for context, NIH provided $5.7 billion dollars for pediatric research that same year. It should be noted that these categories are not mutually exclusive; the same research project could fall under more than one category. Also, many of these funded projects are not directly relevant to clinical research involving pregnant and lactating women. For example, in 2017, NIH estimated that only 13 percent of projects in the "pregnancy" category and 9 percent in the "lactation" category were directly relevant to clinical research involving pregnant and lactating women. Most of the projects were relevant, but not directly related, such as projects on the underlying physiological aspects of pregnancy and/or lactation (PRGLAC, 2018).

has been deemed necessary for studying off-patent drugs for use in pediatric populations and for repurposing drugs for new indications.

Similar to conducting research on off-patent medical products for pregnant and lactating women, there are few financial incentives to support drug repurposing for an off-patent drug or to conduct clinical research on off-patent drugs for pediatric use (Austin et al., 2021; Haslund-Krog et al., 2021). Owing to the lack of incentives for drug repurposing, there has been a call to increase government investment, specifically from NIH, to fund the necessary studies to expand a drug's indications (Sachs et al., 2017). In the case of pediatrics, Congress has already responded with the passage of the Best Pharmaceuticals for Children Act (BPCA). The BPCA created an NIH program to fund studies of off-patent drugs within pediatric populations, which has successfully completed over 45 trials and led to 19 product labeling changes (NIH, 2023a). NIH funding to study off-patent medical products in pregnant and lactating women could support much needed research for these populations.

Public-sector investment in research for pregnant and lactating women can lead to indirect benefits for researchers and research institutions that may address other dissuasive factors discussed above. Owing to the influence of government funding in research, increases in public investment can attract researchers who have an interest in aligning their

research pursuits with the priorities of funders (Whitley et al., 2018). Increased NIH funding in research on pregnant and lactating women and related career development opportunities would signal to researchers across the scientific community that research in this area could offer a financially viable career path, as has been demonstrated with funding for Alzheimer's research (Katiyar et al., 2021).

Further, consistent evidence demonstrates that government funding for biomedical and clinical research paves the way for future research developments from private industry (NRC, 2011). Publicly funded clinical research can produce generalizable knowledge regarding research processes and techniques that industry can use to inform its own clinical research. Public investment in research is also a valuable mechanism that enables funded researchers to develop skills and capacity that can be translated to future studies funded by industry or other sources (Scherer, 2000).

Conducting federally funded studies with pregnant and lactating women may also function to ease some of the expected challenges of beginning to do research with pregnant and lactating women. Federal agencies beyond NIH, including the Agency for Healthcare Research and Quality (AHRQ), Centers for Disease Control and Prevention (CDC), and Department of Defense (DoD) currently fund and/or conduct clinical research with pregnant and lactating women (PRGLAC, 2018). As federally funded researchers innovate and disseminate approaches to include pregnant and lactating women in clinical research more safely, the entire clinical research ecosystem could benefit from the findings obtained from public investments to conduct further research. For example, after the implementation of the BPCA in 2002, NIH began awarding contracts to individual academic centers to study drug safety and efficacy, and to conduct pharmacokinetic studies (Greenberg et al., 2022). However, pediatric trials are ethically complex, (Laventhal et al., 2012) often underpowered, and require special considerations to conduct the research in a timely and efficient manner. Therefore, after several years, NIH created the Pediatric Trials Network (PTN) to develop a more coordinated, succinct approach to conducting pediatric trials (Greenberg et al., 2022). Lessons learned on conducting pediatric trials through the PTN have informed other pediatric drug networks, such as the Global Pediatric Clinical Trials Network, helping to advance drug development in children. A similar approach may help advance research in pregnant and lactating women.

Institutional Review Board Decision Making

IRBs are an essential ethical pillar to ensuring that clinical research protects participants; a study that includes human participants cannot proceed without IRB approval. Therefore, IRBs must be able to define the

safeguards necessary for including and protecting pregnant and lactating women in clinical research and be able to determine when such research is appropriate and when it is not. IRBs must be empowered to independently assess whether the research protocol complies with all laws and regulations relevant to the protection of human research subjects (Grady, 2015). If research concerns off-patent medical products for pregnant and lactating women, or if in fact research during any stage in the product life cycle is to proceed, IRBs will need additional guidance and capacity specific to pregnancy and lactation.

A common critique of the IRB system is that IRBs have been overburdened with fulfilling regulatory requirements that provide little value in terms of protecting research participants (Fost and Levine, 2007). These critics have argued that these requirements for IRBs have led IRBs to overemphasize protecting the research institution from regulatory sanctions rather than protecting research participants from harm, while at the same time stifling the advancement of research. IRBs have also received criticism for overinterpreting a commitment to justice as protecting participants from harm, and not focusing enough on the societal responsibility to include subgroups who have been understudied and underrepresented in clinical research (Bierer et al., 2020). Even the HHS Secretary's Advisory Committee on Human Research Protections has acknowledged this failure and in 2021, published a document reconsidering the principle of justice under 45 CFR part 46 (HHS, 2021). To rebalance the priorities of IRBs, they will need guidance on interpreting regulations designed to protect pregnant and lactating women in clinical research.

The 2014 National Academies report *Proposed Revisions to the Common Rule for the Protection of Human Subjects in the Behavioral and Social Sciences* found that there was little information within the Common Rule or related guidance that would help IRBs assess the risks and benefits of clinical research (NRC, 2014). The report found that ambiguity of the minimal risk standard set forth in the Common Rule contributed to inconsistencies in how IRBs interpreted and applied the regulations. The report recommended revisions to the regulations and guidance on minimal risk to provide greater clarity for IRBs and reduce divergent interpretations. The report also addressed the special populations discussed in the Common Rule, including pregnant women, by recommending improved guidance that helps IRBs distinguish between vulnerabilities in participants' lives and their vulnerability to research risks. This committee endorses these recommendations and asserts that additional guidance specific to pregnancy and lactation would assist IRBs in making impartial decisions regarding the inclusion of these populations.

However, there are strategies that investigators and institutions can take to facilitate success with IRB approval and strengthen protocols

when conducting clinical research with pregnant women. In a study on factors that facilitate research with pregnant women, Mastroianni et al. found that research with pregnant women was more likely to receive IRB approval when investigators took steps during the study design process to minimize risks for potential pregnant participants and their offspring and when they requested safety data from drug companies and FDA. Further, consulting with IRBs throughout the study design process was helpful in identifying potential risks, strengthening the protocol prior to submission, and navigating IRB rules. Finally, having IRB members with proper expertise in pregnancy and pregnancy research was cited as an important factor in conducting research with pregnant women. This might involve formal IRB training on assessing risks on conducting research with pregnant women or including an obstetrician as an IRB member (Mastroianni et al., 2020).

On-Market, On-Patent Products

The manufacturer of a single-source drug (i.e., one without generic competitors) has a financial interest in maintaining its exclusive marketing position for as long as legally feasible. Exclusivity allows the manufacturer to sell its product without competition from generic or biosimilar products, thereby allowing the patented product manufacturer to set prices as a function of what it thinks the market will bear based on product value, the amount needed to recuperate the financial costs of developing the product (as well as the costs of research for other products in the development pipeline that never make it to market), and its safety and effectiveness profile compared to therapeutic alternatives. Because of the importance that manufacturers place on exclusivity, Congress has previously used exclusivity to incentivize medical product companies to conduct certain studies or to develop certain products. Congress has developed several mechanisms to create incentives through extensions of patent and market and data exclusivity periods, including priority review vouchers, the Orphan Drug Act, and the Best Pharmaceuticals for Children Act (BPCA).

In 2007, Congress authorized FDA to award priority review vouchers to drug companies that had developed drugs and received approval for tropical diseases,[3] and subsequently authorized priority review vouchers for drugs to treat rare pediatric diseases and medical countermeasures.[4,5]

[3] *Priority review to encourage treatments for tropical diseases.*, 21 U.S.C. 360n. (2013).

[4] *Priority review to encourage treatments for rare pediatric diseases,* 21 U.S.C. 360ff. (2013)

[5] *Priority review to encourage treatments for agents that present national security threats,* 21 U.S.C. 360bbb-4a. (2016).

Priority review vouchers achieve extended patent exclusivity by allowing drug companies to use the voucher to shorten FDA's review timeline for a product that they submit for approval in the future, enabling that product earlier market entry with more time remaining on the patent (Kesselheim et al., 2015). However, priority review vouchers have had little to no effect on drug development in the areas for which they are available (GAO, 2020).

There has long been a lack of available treatments for rare diseases because the small population for each indication translated to poor return on investment for drug developers. A 7-year extension on market exclusivity was granted through the Orphan Drug Act for products that would not be otherwise developed owing to small patient populations. However, extended market exclusivity and lack of competition in the sector allowed industry to charge prices that were unaffordable for many patients. Less than 10 percent of patients receive treatment with these drugs because of the cost of medications. Experience with the Orphan Drug Act has demonstrated that without properly tailored exclusivity, patients' access to treatments may be hindered until exclusivity expires and lower priced generics are introduced (Tu, 2023).

The BPCA provides a particularly relevant example of how to use patent and data exclusivity to incentivize the conduct of clinical studies for a specific population once the medical product is already on the market. Unlike priority review vouchers or the Orphan Drug Act, the BPCA targets incentives to drugs that are approved and on-patent but do not have data on the drug's use in a defined population—children (see Box 5-2).[6] The BPCA appears to be an enticing incentive for some sponsors. Thirty-five percent of sponsors who received a voluntary request to perform pediatric studies in exchange for extended exclusivity did so (Carmack et al., 2020). The incentive contributed to pediatric labeling changes in over 60 drugs between 1998 and 2018 (Bourgeois and Kesselheim, 2019).

The implementation of the BPCA has not been without its shortcomings, and there are numerous proposed solutions to remedy these challenges. On average, it takes sponsors 7 years from product approval to complete studies in a pediatric population (Carmack et al., 2020). This is partially because, like trials with pregnant and lactating populations, recruitment of children is more difficult than for nonpregnant adults, and pediatric trials often struggle to sufficiently power studies (Joseph, 2015). Furthermore, sponsors have tended to delay their response to FDA's request for pediatric studies toward the end of patent exclusivity (Olson and Yin, 2018). Extrapolation of efficacy data from adult trials to pediatric

[6] *Best Pharmaceuticals for Children Act*, P.L. 107-109 (2002).

BOX 5-2
Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

For many years, clinicians who treated young children were frustrated by the lack of safety and efficacy information on drugs for children of different sizes and ages. Many of the challenges and barriers for the inclusion of pregnant and lactating women mirror those of pediatric populations prior to legislation being passed, including lack of economic incentives, difficulty recruiting study participants, and concerns around perceived liability of conducting research in this population (IOM, 2012). However, as with pregnant and lactating women, understanding how drugs work in pediatric populations is critical for safely prescribing drugs in children. Although a number of efforts attempted to include more research on pediatric populations over the years, change really began in the late 1990s with the passage of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA).

The BPCA

The BPCA was passed in 2002 and encourages pharmaceutical companies to conduct pediatric studies for drugs that are already on the market, rather than those in the development pipeline, by providing an additional 6-months of marketing exclusivity for those who voluntarily carry out clinical studies in the pediatric population, during which time no equivalent generic drugs can be marketed. Sponsors may apply to FDA to receive the incentive in exchange for conducting pediatric studies, or FDA may issue written requests to sponsors of drugs for which FDA would like pediatric studies to be conducted.

The second element of the BPCA is an off-patent program funded by NIH that has been highly productive for dosing, safety, and efficacy studies for molecules that are used in children but have largely gone unstudied. The off-patent program is not an incentive for industry; it is legislation that authorizes NIH to pay for the research. The NIH-BPCA program is mandated to provide clinical study data to FDA for label change consideration, to sponsor clinical studies of prioritized drugs, and to identify drugs in need of further study.

The PREA

The PREA, which was passed in 2003, authorizes FDA to require pediatric studies on the safe and effective use of new drugs or biologics in children. FDA initially attempted to release its own guidance requiring the submission of a new drug or biologic application contain a pediatric assessment in 1998. However, the FDA guidance was challenged in court and the courts ruled against FDA. Therefore, key provisions from the FDA guidance were adopted into law with the passage of the PREA.

Outcomes

The combined goals of the BPCA (incentive) and the PREA (enforcement) have been an effective strategy. In a status report discussing the effect of the legislation

BOX 5-2 Continued

in the 5 years between 2015 and 2020, FDA noted that efforts had advanced the availability of pediatric use information on labeling for approved drugs and moved planning for pediatric inclusion in clinical studies earlier in the development process (FDA, 2020). As of September 2022, more than 1,000 drugs and biologics had undergone labeling changes to include pediatric use information as a result of the PREA, the BPCA, and the 1998 Pediatric Rule (FDA, 2022).

populations is a developing field of regulatory science, which may help to speed pediatric drug development and reduce the number of pediatric participants that need to be enrolled in clinical trials (Sun, 2017). In a sample of the BPCA and PREA labeling changes that used extrapolation, researchers found that the more that FDA accepted extrapolation in a labeling change, the more likely a label change occurred for pediatric populations (IOM, 2012).

Since the BPCA offers a blanket 6-months of exclusivity, drugs that have a large market in adults may benefit more from the incentive than a product that is more frequently used in pediatric populations (Bourgeois and Kesselheim, 2019). An additional critique has been that the exclusivity applies to the active pharmaceutical ingredient rather than the product, which is exemplified in the particularly stark case of Viagra benefiting from the patent extension because it shares the active pharmaceutical ingredient sildenafil with a pulmonary arterial hypertension drug. A policy analysis of the BPCA encouraged Congress to amend the BPCA, including the prioritization of incentives to research products of highest benefit to children and adopting a tiered incentive that favors sponsors that complete studies in a timely manner (Bourgeois and Kesselheim, 2019). An incentive program that rewards manufacturers for conducting additional clinical studies for pregnant and lactating women could effectively compensate for sponsors' fear of incurring liability for conducting these studies by building on the successes and learning from the challenges of the BPCA.

Payers

Clinical trial results are a critical component in determining coverage decisions by payers, such as private insurers, Medicare, and Medicaid. Theoretically, some payers could use the coverage determination process to encourage product manufacturers to conduct research with pregnant and lactating women and could even restrict coverage unless

further evidence on dosing, safety, and efficacy was available in these populations. However, the committee does not make recommendations targeting this process because it would limit patients' ability to access medical products they may need, particularly for pregnant and lactating patients.

One promising approach that has been used to generate evidence in certain subpopulations while not limiting access to medical products is the Centers for Medicare and Medicaid Services (CMS) coverage with evidence development (CED) paradigm. CED determination allows for Medicare to provide coverage for "items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data" (CMS, 2023). For example, in 2022, CMS issued a national coverage determination for a medication to treat Alzheimer's disease under CED, which allows coverage of the medication for patients enrolled in a clinical trial approved by CMS or supported by NIH. CMS highlights the "disappointing lack of inclusion of underserved populations" in their coverage determination memo and requires diversity as a key protocol requirement (CMS, 2022). However, national coverage determinations, which allow for CED determinations, are only made for Medicare and are not made for Medicaid, since Medicaid is a federal-state entitlement program that relies on states to purchase drugs on behalf of Medicaid beneficiaries (CRS, 2014).

According to the federal Medicaid and CHIP Payment and Access Commission, Medicaid directors have asked CMS for the flexibility to apply similar CED determinations in their own states (MACPAC, 2019). However, CMS does not explicitly have the authority to grant that request and a statutory request is necessary to ensure states can implement coverage criteria similar to Medicare. In 2023, the Medicaid and CHIP Payment and Access Commission voted to approve a recommendation that calls on Congress to allow states to follow CED requirements included in Medicare coverage determinations (MACPAC, 2023). If states are allowed to create CED determinations, this could be a powerful tool for generating evidence on the dosing, safety, and efficacy of medical products in pregnant and lactating women, should states choose to use it. However, until congressional action is taken, CED determinations will remain an option only for Medicare beneficiaries.

Products in Development

Currently, there is little financial incentive for pharmaceutical companies to conduct clinical studies in pregnant and lactating women before drug approval. As described above, priority review vouchers and the Orphan Drug Act are examples of incentives designed to spur research

and the development of new products for disease areas that have not received adequate investment. Both programs are intended to address disease categories, such as rare pediatric diseases or other rare diseases. While there are conditions specific to pregnancy or lactation (e.g., preeclampsia, gestational diabetes, low milk production) for which additional available treatments would be beneficial, most of the conditions common in pregnant and lactating women do not neatly fit into prespecified disease categories. Therefore, it would be difficult to implement a similar incentive that aims to encourage product development within a specific disease category.

Incentives are not the only policy tool that can induce product development. FDA has substantial discretion to determine what studies are necessary to evaluate safety and effectiveness. However, FDA does not have sufficient authority under current law to mandate studies in pregnant and lactating women. In the Pediatric Research Equity Act (PREA), Congress expressly authorized FDA to require studies in pediatric populations, who, like pregnant and lactating women, had long been prescribed medications without adequate evidence (see Box 5-2).[7] The PREA applies to new drugs and biologics that are in development, and requires that pediatric studies be conducted prior to approval of the product for the adult population, though FDA can grant sponsors a deferral or waiver of the requirement. Studies conducted under the PREA have resulted in 532 labeling changes from its enactment in 2003 through 2018 (Bourgeois and Kesselheim, 2019). While the PREA has led to far more pediatric labeling changes than the BPCA, both programs have been vital in the development of pediatric data, as each targets a separate stage on the product development pathway.

The PREA has been successful in generating dosing, safety, and efficacy information for pediatric use, but there are opportunities to improve upon its existing framework (IOM, 2012). Under the PREA, pediatric studies can only be required for the indication under review for the general population, even if the mechanism of action suggests that it may be effective in treating another condition prevalent in the pediatric population (Bourgeois and Kesselheim, 2019), though an exemption has been made if a drug is a promising candidate for treating pediatric cancers.[8]

Many new drugs in development are for rare diseases and thus receive exemptions from conducting pediatric studies (Bourgeois and Kesselheim, 2019). While there are challenges to conducting pediatric studies for these drugs given the small patient populations, the waivers

[7] *Pediatric Research Equity Act of 2003,* P.L. 108-155. (Dec. 3, 2003).
[8] *FDA Reauthorization Act of 2017,* Pub. L. No. 115-52, § 504. (Aug. 18, 2017).

for orphan drugs deprive children of information on these drugs' safety and effectiveness. Because deferrals can be granted under the PREA if the drug product is ready for approval in the general population, many sponsors receive at least one deferral, and some receive multiple (Bourgeois and Hwang, 2017). This results in most newly approved products being available on the market for many years without any pediatric labeling information (Hwang et al., 2019). In fact, among sponsors required to complete pediatric studies, 34 percent had completed the required studies 7 years after the initial approval.

FDA guidance instructs sponsors to submit their plans for conducting pediatrics studies required under the PREA by the end of Phase II development for the adult population (FDA, 2020), but the deadline for this submission may come too late in the product development process for sponsors to be able to complete pediatric studies before or shortly after product approval (Carmack et al., 2020). Conversely, sponsors in the European context have critiqued the timing of pediatric investigation plans—which are required to be submitted to the European Medicines Agency by the end of Phase I for the adult population—for being premature in the development process and requiring follow-up modifications (Rei Bolislis et al., 2021). Improvements in FDA's enforcement capacity have been proposed to address these challenges with timely study completion (Bourgeois and Kesselheim, 2019; Hwang et al., 2019). Despite the difficulties with the PREA implementation and enforcement, a similar requirement for studies in pregnant and lactating women for medical products in development could be an effective strategy for developing adequate product labeling for these populations.

CONCLUSIONS

Conclusion 5-1: Many factors influence perceptions of legal liability and factor into stakeholder decisions about whether to include pregnant and lactating women in clinical research. Some factors may dissuade decision makers from pursuing clinical research that includes pregnant and lactating women, while others may be persuasive.

Conclusion 5-2: Financial incentives can be a powerful counterbalance to the dissuasive factors that sponsors, researchers, research institutions, and other stakeholders weigh in their decisions concerning inclusion of pregnant and lactating women in clinical research.

Conclusion 5-3: A legal requirement that sponsors conduct clinical studies in pregnant and lactating women would advance product labeling information on the safety, efficacy, and dosing of medical products for these populations.

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6

Recommendations

Based on the information provided through public testimony and our own research and deliberations, the committee makes nine recommendations to improve the responsible and ethical inclusion of pregnant and lactating women in clinical research while mitigating the risk of legal liability. These recommendations take three interconnected approaches to reducing liability risks associated with including pregnant and lactating women in clinical research—and to aligning perceptions of the liability of including these populations in clinical research with the evidence. The first entails strategies that directly mitigate liability; the second is through minimizing potential harm to research participants and thereby reducing the grounds for liability; and the third aims to allay the concerns that discourage researchers and sponsors from including pregnant and lactating women in clinical research which, as elaborated in Chapter 5, are factors that are weighed alongside the potential for liability These three strategies are interconnected, as mitigating liability and reducing potential harm will also improve and address perceptions of liability. The committee's nine recommendations attend to the interests and concerns of the multiple stakeholders and decision makers involved along the medical product development pathway.

In some ways, the goals of the recommendations overlap. This redundancy is intentional. The recommendations addressed to the authority that existing entities have allows them to act in a timely fashion to implement the proposals. These steps can be expanded when, as we recommend, Congress passes legislation that can enhance existing powers and

provide greater accountability for the stakeholders involved, but we recognize that enacting such changes can take time. As noted in Chapter 1, it is critical that research involving pregnant and lactating women be started promptly, with the understanding that further changes will need to address all the challenges to conducting such research. Therefore, while achieving the safe and ethical inclusion of pregnant and lactating women in clinical research while mitigating liability risks is the unifying goal of this report, the recommendations are written so each one can stand alone and contribute to overcoming the barriers to the inclusion of pregnant and lactating women in clinical research.

PROVIDE GREATER REGULATORY CLARITY

Clear guidance from the U.S. Food and Drug Administration (FDA) can provide a pathway for critical stakeholders directly engaged in clinical research (e.g., sponsors, clinical investigators, and institutional review boards [IRBs]) to enhance the conduct of research with pregnant and lactating women that minimizes the risk of harm that may be anticipated by that research. By minimizing potential harm, this guidance also mitigates potential liability associated with that harm. While compliance with regulatory requirements does not necessarily preclude a finding of negligence or other failure to behave responsibly, compliance with those requirements may be an important consideration in determining whether a failure of duty did or did not occur (American Law Institute, 2023). Regulatory clarity and consistency are paramount to medical product sponsors and may influence decisions to pursue any particular type of research, including studies involving pregnant and lactating women (Seiguer and Smith, 2005).

In addition to compromising the reassurance regarding liability that sponsors and investigators may achieve by adhering to FDA's regulatory expectations, uncertainty can also prolong the time and increase the costs of research and development and ultimately delay product approval (Hoerr, 2011; Stern, 2017). Predictable outcomes are important to research investors and funders (Hoerr, 2011; Seiguer and Smith, 2005), who aim for a speedy regulatory approval of their product in order to capitalize on patent exclusivity before the market opens to competitors.

In the absence of clear guidance from regulators, research sponsors may try to mitigate the risk of regulatory delays and rejections by avoiding the conduct of studies with pregnant and lactating women. As exemplified throughout this report, 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 pregnant and lactating women, including the timing of those 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 to improve sponsors' understanding of FDA expectations.

As noted in Box 3-2, as part of the PDUFA VII Commitments, FDA plans to update its framework and guidance on pregnancy postmarketing requirements and commitments. These ongoing efforts by FDA are an important step to clarifying guidance for noninterventional studies involving pregnant women. In regard to the timing of studies that include pregnant and lactating women, FDA may consider whether certain conditions, such as the development of a treatment or vaccine in response to a pandemic, merits inclusion of pregnant and lactating women earlier in the product development pathway. However, the committee emphasizes that the approval of a medical product for the general population is not to be contingent on the completion of clinical studies in pregnant and lactating women.

Recommendation 1. 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.

a. **The revised guidance should set forth the study designs, safeguards, and product-specific monitoring expected for conducting clinical studies with pregnant and lactating women and include considerations for how sponsors should determine appropriate study designs, safeguards, and product-specific monitoring.**
b. **The revised guidance should make clear that research plans and all necessary study protocols are prepared, research sites are identified, and monitoring and oversight committees are appointed for pharmacokinetic, pharmacodynamic, and dosage determination studies with pregnant**

and lactating women while Phase III studies for the product are being carried out in the general adult population.

c. The revised guidance should specify contents of a streamlined Investigational New Drug Application for use by academic and other noncommercial sponsors to study a drug in pregnant and lactating women in the event that studies are not initiated and completed in a timely manner by the New Drug Application, Biologics License Application, or Premarket Approval holder as contemplated by the guidance.

d. The revised guidance should make clear the requirement to conduct studies with pregnant and lactating women is dependent upon (i) the product having the potential for use by pregnant and lactating women and (ii) that use being consistent with available clinical and preclinical safety and efficacy data in these populations. If the product sponsor believes that data from preclinical studies of the product, or evidence concerning the safety of other products in the same class, raises concerns about the potential harm to pregnant and lactating women or their offspring, the sponsor may submit to FDA a justification for not including pregnant or lactating women in the clinical studies outlining the basis for such for concerns and why the potential harms cannot be adequately prevented or mitigated in light of the potential benefits to these populations. If FDA reviewers agree with the justification, trials in pregnant or lactating women are not to be carried out and the safety information must be included in the drug labeling.

The federal government has long acknowledged the need to improve the diversity of clinical research (NASEM, 2022). With the passage of the National Institutes of Health (NIH) Revitalization Act in 1993, Congress affirmed that federally sponsored research needed to improve its inclusion of women and racially and ethnically minority populations, who had long been historically excluded and disproportionately underrepresented in clinical research. Congress renewed its commitment to the inclusion of more diverse populations in clinical research through the requirement for medical products sponsors to develop diversity action plans, enacted in the Food and Drug Omnibus Reform Act (FDORA).[1,2] The legislation gives FDA the authority to require diversity action plans from sponsors, which are intended to detail the sponsors diversity goals and

[1] Food and Drug Omnibus Reform Act (FDORA), (2023).
[2] *Consolidated Appropriations Act,* (2023).

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. As of the start of 2024, FDA is still in the process of developing its guidance and has yet to publicly release draft guidance on the implementation of diversity action plans.

Including pregnant and lactating women as categories in diversity action plans would ensure that sponsors consider these populations at the beginning of the clinical development process. Although this only applies to new medical products in development and not products with FDA approval, this helps start the process of conducting research with these populations. Furthermore, conversations between sponsors and FDA regarding plans to include pregnant and lactating women in clinical studies would promote information exchange about appropriate study designs and safeguards. Requiring the 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.

Likewise, the availability of preclinical data from development and reproductive toxicology (DART) studies can help sponsors, in coordination with FDA, to identify and minimize potential safety risks before pregnant or lactating women are exposed to medical products. It is essential that DART studies be conducted as early as can feasibly be done to generate preclinical data capable of guiding decisions regarding clinical studies with pregnant and lactating women. If DART studies reveal a potential safety signal, it may be appropriate for FDA to request that the sponsor conduct additional toxicology studies to further evaluate the signal.

Furthermore, it is critical that as more research studies involving pregnant and lactating women are conducted, that there is diverse representation within those populations. As the 2022 National Academies report *Improving Representation in Clinical Trials and Research* found, there has been progress with the representation of White women in clinical research; however, progress has largely stalled in attaining racial and ethnic diversity in clinical research. The lack of racial and ethnic diversity compounds health disparities and inequities, hinders innovation, reduces already low accrual rates, and undermines public trust (NASEM, 2022).

These disparities are particularly pronounced in pregnant populations, with Black and American Indian and Alaskan Native (AIAN) populations having pregnancy-mortality rates that are about three and two times higher, respectively, when compared to White women (Hill et al., 2022). Because of systemic and structural factors, disparities also exist for lactating individuals, with rates of breastfeeding initiation significantly lower for non-Hispanic Black populations and AIAN individuals compared to overall breastfeeding rates (CDC, 2023). Therefore, it is crucial

to consider the inclusion of pregnant and lactating women as part of an intersectional diversity action plan that is reflective of the populations disproportionately burdened by the disease process in question and the entire population in which the medical product may eventually be used.

Recommendation 2. The U.S. Food and Drug Administration (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. FDA should revise its guidance relating to such diversity action plans to include the following:

a. **Formal discussion, such as during meetings before an Investigational New Drug Application is granted, on FDA's expectation for the inclusion of pregnant and lactating women in clinical trials of the product and on the sponsor's plans to include these populations in clinical trials.**
b. **Submission of, or if already completed, reference to relevant preclinical data that support the determination of dosage, safety, and efficacy in pregnancy and lactation, including developmental and reproductive toxicology studies and, as available, any safety data on pregnancy and lactation for other drugs in the same class. If the preclinical data presented in the diversity action plans raises safety concerns for conducting human trials in pregnant and lactating women, a justification for not conducting clinical studies must be submitted along with the diversity action plan outlining the evidence for concerns. When FDA reviewers agree there are safety concerns regarding clinical testing in pregnant and lactating women, trials are not to be completed and the safety information must be included in the drug labeling.**
c. **Plans for conducting pharmacokinetic and pharmacodynamic studies in pregnant and lactating women, including dosing studies through each stage of pregnancy. The plans for these studies should be submitted to the agency no later than the submission of a New Drug Application or Biologics License Application for the general population.**

IRBs serve as the gateway to human subject research, and the ability to conduct research that includes pregnant and lactating women is incumbent on the willingness of IRB members to approve such research.

Unfortunately, many IRB members lack the training or guidance to assess the risks and benefits of research with pregnant and lactating women (Blehar et al., 2013; Lyerly et al., 2008; Saenz et al., 2017; van der Zande et al., 2016). Because of IRBs' lack of familiarity with research proposals that include pregnant and lactating women, they may be unable or unwilling even to consider approving such a proposal (Saenz et al., 2017). Furthermore, IRBs vary widely in their interpretation of title 45 of the *Code of Federal Regulations,* part 46, which codifies protections of the rights and welfare of human participants in research, as discussed in Chapter 3. Specifically IRBs may have different interpretations in regard to what "minimal risk" entails in Subpart B of the regulations, which provides additional protections for pregnant women, human fetuses, and neonates (White et al., 2021). IRBs may also vary in whether breastfeeding children of lactating research participants are considered research participants (HHS et al., 2022). If children of lactating research participants are also considered research participants, then Subpart D of the regulations would apply, which provides additional protections for children.

The Office for Human Research Protections (OHRP) has not issued guidance on pregnant and lactating women as research subjects, including guidance for IRBs on interpreting Subpart B nor on the applicability of Subpart D to these populations. In practice, the lack of regulatory clarity often results in conservative interpretations by decision makers that discourage conducting research with pregnant women (Blehar et al., 2013; Mastroianni et al., 2017).

The denial of proposals for research involving pregnant and lactating women further erodes the opportunities for researchers to pursue work in this area and leads to a lack of knowledge, funding, and ultimately, a lack of a trained workforce with expertise in these areas. The current system creates a vicious cycle that undermines the development of knowledge and innovation for the care of pregnant and lactating women.

There are many stakeholders that play a role in educating and promoting research with pregnant and lactating women, including research institutions, professional organizations, educational providers, and community-based nonprofit organizations. The list includes, but is not limited to the following:

- American College of Obstetricians and Gynecologists
- Association of Women's Health, Obstetric and Neonatal Nurses
- Academy of Breastfeeding Medicine
- American Academy of Pediatrics
- Society for Maternal–Fetal Medicine
- Public Responsibility in Medicine and Research
- American College of Clinical Pharmacy

- American Society of Health System Pharmacists
- Collaborative Institutional Training Initiative
- Liaison Committee on Medical Education
- Society for Women's Health Research

These groups can provide education and training for IRB staff and committee members, research faculty, and professional and graduate students. For example, the American College of Obstetricians and Gynecologists has released a committee opinion titled "Ethical Considerations for Including Women as Research Participants" that includes a section on risks and benefits, study design, and informed consent within the context of research with pregnant women.

Recommendation 3. 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.

a. **OHRP should issue guidance that provides definitions and interpretation for 45 CFR 46, Subpart B, particularly "minimal risk" and "additional safeguards" that are conducive to the responsible and ethical inclusion of pregnant and lactating women in clinical research.**
b. **OHRP should issue guidance to clarify the applicability of 45 CFR 46, Subpart D, for clinical research that enrolls lactating women who breastfeed their children during the study.**
c. **OHRP should issue a list of frequently asked questions that could assist clinical researchers and IRBs to assess risk in clinical research that involves pregnant and lactating women and to provide justifications for the inclusion or exclusion of pregnant or lactating women in clinical research.**
d. **OHRP guidance should, like FDA guidance, recommend that IRBs have experts in pregnancy, lactation, and neonates**

participate in the review of study protocols involving such participants.

e. **The OHRP Division of Education and Development should offer training and outreach for researchers and IRBs to develop expertise in research in pregnancy and lactation.**

f. **OHRP should create a subcommittee for research with pregnant and lactating women within the Secretary's Advisory Committee on Human Research Protections that will provide detailed recommendations on how to conduct more research with pregnant and lactating women safely and ethically.**

PROVIDE INCENTIVES, FUNDING, AND ACCOUNTABILITY FOR RESEARCH

As described in Chapter 5, legislation passed in the early 2000s has helped to overcome challenges in conducting research in pediatric populations that have similarities to the challenges faced by research with pregnant and lactating women. The committee considered the models for spurring innovation in pediatric populations—the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)—as well as other policies to incentivize medical product development, and whether similar initiatives might be helpful with pregnant and lactating populations. The BPCA and the PREA serve incentive and requirement functions in increasing pediatric research. The BPCA provides the incentive through a patent extension or provision of public funds for research for products that are off-patent, and the PREA provides the requirement, by establishing a regulatory mandate for sponsors of new products, to collect preclinical and clinical data in pediatric populations. The committee concludes that this coupling of incentives and accountability would likewise spur research in clinical studies on the dosage, efficacy, and safety of drugs, biologics, and vaccines, as well as the efficacy and safety of devices for pregnant and lactating women.

However, the committee acknowledges that while it believes an approach that incorporates an incentive and requirement would be beneficial for driving clinical research in pregnant and lactating women, there are fundamental ethical and regulatory differences between pregnant populations, lactating populations, and pediatric populations that should be acknowledged before applying that approach. First, children are not usually part of the population for the indications that FDA approves as a drug first enters the market. Therefore, to get a pediatric indication, sponsors must submit additional clinical trial data in pediatric populations. However, unlike children, pregnant and lactating women are considered

part of the general adult population for which an adult indication is approved, meaning that for a drug that is approved for general use, it is approved for use in pregnant and lactating women. A prescription for a pregnant or lactating woman of any drug approved for adults, unless it is specifically contraindicated for use in pregnant and lactating women, is considered "on-label" even when there are not data on appropriate dosage and timing, or even on safety and efficacy for such persons.

The committee is not recommending that a separate regulatory category be created for pregnant and lactating women, since that would make the use of most licensed drugs "off-label" for pregnant and lactating women and markedly restrict access for those patients. However, it is important to note that sponsors lack the additional incentive of an expanded indication in conducting clinical studies in pregnant and lactating women that exists with pediatric studies under the PREA and the BCPA. While falling short of a new indication, the Pregnancy and Lactation Labeling Rule (PLLR), finalized by FDA in 2014, requires sponsors to include a descriptive summary of data relevant to pregnancy and lactation on the product label (Appendix D).[3] However, nearly a decade after the implementation of the PLLR, there has been little to no increase in the number of products that have collected human data on pregnancy and lactation when compared to products approved prior to PLLR implementation (Byrne et al., 2020). This makes other incentives such as extended exclusivities all the more valuable in the context of the pregnant and lactating population.

Another key difference is that children are defined as persons who have "not attained the legal age for consent to treatments or procedures involved in clinical investigations." The purpose of using the BPCA and the PREA as a model is not, in any way, to suggest that pregnant and lactating women are a vulnerable population or to suggest that they are not capable of providing consent. Instead, several of the factors that contribute to the lack of clinical research in pregnant and lactating women bear similarities to the challenges faced in spurring clinical research for pediatric populations. Lessons learned from pediatrics show that incentives and accountability measures work and may be similarly effective in spurring medical research for pregnant and lactating women.

The committee acknowledges that experience with the BPCA and the PREA reveals limitations within those frameworks and that there are challenges with the BPCA and the PREA that are likely to also occur in pregnant and lactating women. These include the long wait times for studies conducted under the PREA to be completed, resource challenges for FDA to review all letters of interest from sponsors under the BPCA, and delays

[3] Appendix D can be viewed online at https://nap.nationalacademies.org/catalog/27595.

in translating clinical data collected into labeling changes. Evidence from pediatrics and other areas where postmarketing studies are required also reveals that studies initiated after product approval is received are slower or less likely to be completed (Hwang et al., 2018; Shahzad et al., 2023). Nonetheless, since their enactment in 2002 and 2003, the BPCA and the PREA have led to the labeling of over 1,000 products with pediatric-specific information (FDA, 2022). Labeling changes of that magnitude could make a tremendous difference in reducing uncertainty and potential harm for pregnant and lactating women using medical products.

Despite certain limitations and key differences between pediatric and pregnant and lactating populations, the BPCA and the PREA do serve as useful models for the type of legislation that would provide FDA with the necessary authority to impose requirements for additional study with pregnant and lactating women while also providing incentives needed to stimulate additional research with pregnant and lactating women.

The data generated through clinical studies conducted under the BPCA and the PREA have promoted the health of children who now have access to medical products supported by high-quality evidence. Were Congress to enact programs to increase the development of evidence for the care and treatment of pregnant and lactating women modeled on the BPCA and the PREA, the health of pregnant and lactating women and their fetuses and children would be promoted in a similar way as when Congress prioritized the health of children over 2 decades ago.

Incentives Modeled on the BPCA

The case law data presented in Appendix B and described in Chapter 2 of this report indicate that, based on reported cases, there is limited liability in clinical trials for pregnant women and virtually no liability for lactating women. The case law data indicate that sponsors may actually face considerably more risk of liability for harms related to pregnant women's use of FDA-regulated products once the product has been approved and is available in the open market. While sponsors are required to submit to FDA postmarketing safety reports and may be subject to postmarketing requirements or commitments—which may be fulfilled through a pregnancy registry,[4,5] there is little indication that sponsors wish to conduct the trials that might indicate future risks once a drug is already on the market.

Chapter 5 explores other factors that might contribute to the reluctance to include pregnant and lactating women in research. One such factor is that

[4] *Postmarketing reporting of adverse drug experiences* 21 CFR 314.80.
[5] *Postmarketing reporting of adverse experiences.* 21 CFR 600.80.

there is little to no financial incentive for sponsors to conduct this research, and there are no requirements to do this research outside of occasional postmarketing requirements imposed by FDA when there is a known serious risk or available data indicate the potential for a serious risk. Providing concrete financial incentives for sponsors is an important mechanism to tip the scales in favor of conducting research in pregnant and lactating women, particularly as sponsors weigh the financial risk of a potential increase in liability for greater use of their product postapproval in pregnant women. As with the pediatric experience, a financial incentive may encourage sponsors to take what would otherwise be costly and potentially unprofitable steps to begin research with pregnant and lactating women.

There is virtually no incentive for product sponsors to conduct additional research once a drug is off-patent, as their limited profits would not offset the costs of such research. Here too, the BPCA provides a useful model for stimulating studies with pregnant and lactating women. Instead of incentivizing sponsors to conduct research in this context, the BPCA provides public funds to aid and incentivize clinical researchers and their institutions to do the needed research. Under the BPCA, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has developed a process for prioritizing medical products to be studied with public funding (FDA, n.d.). In response to the PRGLAC Implementation Plan recommendations 8B and 9A, NICHD has begun the process of identifying priorities for medical products to investigate similar to the approach under the BPCA (NIH, 2023d; PRGLAC Task Force, 2020). Also modeled on the BPCA approach, NICHD has released a request for nominations to identify priority medical products to address knowledge gaps (NIH, 2023d). NICHD plans to appoint a committee of external experts to evaluate the nominations and develop a preliminary priority list, which will be refined in a stakeholder meeting.

In addition, the BPCA requires that the data from those studies be submitted to the U.S. Department of Health and Human Services (HHS) and FDA for review, be made available in the public domain, and if appropriate, FDA will negotiate with the holder of the relevant applications for a label change. An incentive and funding mechanism similar to the BPCA, which was codified through amendments to the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act,[6] can make decisions to include pregnant and lactating women in clinical research more appealing to sponsors, investigators, and research institutions.

The committee acknowledges that incentives for the pharmaceutical industry, such as extended market exclusivity or tax breaks, are not

[6] *Best Pharmaceutical for Children Act.,* P.L. 107-109, (Jan. 4, 2000).

without cost for patients or for the U.S. taxpayer, owing to the high-cost of brand-name prescription drugs (Kesselheim, 2017). Further, longer patent extensions, such as the 7-year extension offered through the Orphan Drug Act, have been criticized for the high prices of orphan drugs and their potential to threaten insurance premiums (ICER, 2022). Additionally, the Orphan Drug Act has led to overuse of the "orphan drug" classification to maximize profits, while preventing more cost-effective therapeutics from entering the market (GAO, 2018; ICER, 2022). Incentives can be designed with appropriate guardrails in place to make them more effective.

While the committee does not have the appropriate expertise to determine the most appropriate incentive for industry, lawmakers could consider a sliding scale for exclusivity depending on the information gathered (e.g., fewer months of exclusivity for pharmacokinetic/pharmacodynamic (PK/PD) studies and longer exclusivity for larger well-controlled studies of safety and efficacy, or a longer period of exclusivity for medical products most likely to be used by pregnant and lactating women, and a shorter period for those with less anticipated use by these populations). Similarly, it may be appropriate for Congress to consider providing more generous incentives for products developed for conditions specific to pregnancy or lactation. In considering the priority of medical products to be studied and eligible for incentives, it will be important for the director of NIH and the FDA commissioner to consider the public health needs for the medical product, availability of information concerning the dosage, safety and effectiveness of the medical product in pregnant and lactating women, whether additional information is needed, and whether new studies in pregnant and lactating women may have therapeutic value.

Recommendation 4. 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. This legislation should:

a. Direct the director of the National Institutes of Health, in consultation with the commissioner of the Food and Drug Administration (FDA) and experts in pregnancy and lactation, to develop and publish annual prioritization lists of both on-patent and off-patent approved medical products for which additional studies are needed to assess the dosage, safety, and effectiveness of the use of the medical products in pregnant and lactating women.

b. Direct the secretary of the Department of Health and Human Services (HHS) to award contracts to entities that have the expertise to conduct clinical studies in pregnant and lactating women to study medical products that are no longer subject to relevant patent or exclusivity protections, thus enabling the entities to conduct studies in pregnant and lactating women of one or more of the off-patent medical products identified in part (a) of this recommendation.

c. Grant the secretary of HHS the authority to make a written request to the patent holder of medical products subject to patent or exclusivity protections to conduct clinical studies involving pregnant and lactating women concerning one or more of the on-patent medical products identified in part (a) of this recommendation.

   i. To incentivize manufacturers to complete these studies, Congress should create incentive programs, such as extended market or data exclusivity or tax breaks, to the holder of the approved application if studies are completed within the requested time frame and data are submitted to FDA for inclusion in product labeling.

   ii. This incentive program should be authorized for an initial 5-year period, with reauthorization based on experience with the program and a determination of whether continuation is necessary.

Accountability Modeled on the PREA

In 1998, FDA published its Final Rule requiring sponsors of drugs and biologics to conduct studies in pediatric populations, but a federal court found that FDA did not have the authority to require pediatric studies in 2002 (FDA, 2016). Subsequently, Congress passed the PREA to grant FDA this authority by amending the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Under the PREA, FDA can *require* drug sponsors to conduct studies and clinical trials when a drug is deemed "relevant" to pediatric populations. The goal of the PREA is to protect pediatric patients from risks to them that might not have been revealed as part of the premarket review for a drug that was developed for an adult population, as well as to develop pediatric dosing. The PREA does not apply to on-market drugs and biologics and is therefore only required for drugs and biologics under development. FDA authority could be expanded to compel the same requirements to conduct clinical studies for pregnant and lactating women.

Although FDA has authority to encourage study and clinical trials with pregnant and lactating women, it can only *require* such studies and trials

> to assess a known serious risk related to the use of the drug involved; to assess signals of serious risk related to the use of the drug; and to identify an unexpected serious risk when available data indicates the potential for a serious risk.[7]

Because pregnant and lactating women are rarely studied as part of premarket review, many risks to pregnant and lactating women 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, effectively experimenting on pregnant and lactating women at the population level.

In considering the potential for unintended consequences for requiring sponsors to conduct clinical studies in pregnant and lactating women, the committee recognizes that there are two scenarios in which it may be appropriate to defer or waive such a requirement. First, if a medical product is ready for approval in the general adult population and the sponsor demonstrates that studies in pregnant and lactating women are being conducted or will be conducted with due diligence and at the earliest possible times, it may be appropriate for FDA to grant a deferral to the sponsor. Second, if the sponsor presents evidence that strongly asserts that the medical product would be unsafe or of no therapeutic value in pregnant and lactating women, FDA could grant a waiver, and the evidence presented by the sponsor would need to be included in the product label.

The committee notes that recommendation 5 is related to, but independent of recommendation 1. Whereas FDA has the authority to develop guidance to communicate its expectations and current thinking—as the committee calls for in recommendation 1—a federal district court has previously ruled that FDA does not have the authority to require clinical studies in a specific population[8]—which is the subject of recommendation 5. The implementation of recommendation 1 would enable FDA to provide sponsors with information on how studies with pregnant and lactating women are to be conducted but stops short of requiring those studies to be completed. Recommendation 5 thus tasks Congress with granting

[7] *Postmarketing studies and clinical trials-implementation of Section 505(o)(3) of Federal Food, Drug, and Cosmetic Act*, FDCA 505(o)(3)(B), (Oct. 25, 2019).

[8] *Association of American Physicians and Surgeons, INC v. FDA,* 226 F.Supp.2d 204 (D.D.C., 2002).

FDA the authority to require certain clinical studies be conducted with pregnant and lactating women.

Recommendation 5. 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.

- **a. Congress should direct the secretary of the Department of Health and Human Services to require any entity that submits an application for a new drug, biologic, vaccine, or medical device, or a supplement for a new indication, new dosage form, new dosing regimen, or new route of administration, to submit data on the dosage, administration, safety, and effectiveness of its use in pregnant and lactating women.**
- **b. Congress should amend Section 505(o)(3)(B) of the Federal Food, Drug, and Cosmetic Act to include "(iv) to identify and characterize risks to pregnant and lactating women and their offspring" as a justification for requiring postmarketing studies and postmarketing clinical trials.**
- **c. To ease the initial challenges that may be faced in implementing this requirement, Congress should create programs, such as extended market exclusivity or tax breaks, for the holder of an approved New Drug Application, Biologics License Application, or Premarket Approval when studies are completed within the required time frame and data are submitted to FDA for inclusion in product labels. These programs should expire after several years, once sponsors have experience conducting these studies.**

Provide NIH Funding for Research

Research that includes pregnant and lactating women has been avoided or deprioritized along the medical product development pathway. As the largest supporter of biomedical research, NIH has a responsibility to encourage and stimulate research in these populations. There is a need to increase basic knowledge of how pregnancy and lactation affect how the body handles and responds to drugs to guide and support future research, and to fund and facilitate research that includes pregnant and lactating women when appropriate. NIH could play a particularly important role in funding research in pregnant and lactating women for

off-patent products, given the lack of incentives for sponsors discussed earlier in this chapter. Research on pregnancy, childbirth, and lactation receives only a small portion of overall NIH funding (NIH, 2023b).

Despite high rates of maternal and infant morbidity and mortality in the United States, funding for research in this area has historically been low in both the United States (Smith, 2023) and the United Kingdom (Manningham-Buller and Brocklehurst, 2022). Implicit in the two recommendations in this section is that NIH will need to reevaluate its funding priorities and potentially increase its budget requests to provide clinical research with pregnant and lactating women the necessary attention. While greater efforts are needed, the committee acknowledges that NIH has begun to take important actions in this area, including several research networks (see Box 5-1).

In addition to these NIH initiatives, other federal agencies, including the Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration, and FDA (PRGLAC Task Force, 2018), are carrying out activities to develop essential knowledge, expertise, and capacity in research that involves pregnant and lactating women, but they are only beginning to touch the surface of the needed research for these populations. Greater systemic and sustained support and investment are needed. NIH sets the clinical research agenda, and without leadership, emphasis, and prioritization from NIH, research with pregnant and lactating women will not be prioritized and the status quo—a dearth of knowledge about the effects of most drugs on pregnant and lactating women—will remain unchanged.

The NIH Common Fund presents an opportunity to systematically engage the many institutes and centers within NIH to address a high-priority challenge, such as the paucity of clinical research including pregnant and lactating women (NIH, 2023c). Common Fund programs are designed to harness the resources and expertise across NIH's institutes and centers to respond to NIH priorities that have an opportunity to have a broad impact. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports the most NIH grants for research related to pregnancy and lactation of all NIH's institutes and centers (NICHD, 2018). The creation of an NIH Common Fund program for pregnancy and lactation research would distribute responsibility for supporting this research across NIH's institutes and centers. However, Common Fund programs are time bound and intended to achieve specific goals within a 10-year period. Therefore, NIH-wide efforts to kick-start clinical research in pregnant and lactating women through the Common Fund would need to be coupled with sustainable research initiatives.

Expanding existing NIH networks can promote sustained infrastructure to conduct research in pregnant and lactating women to answer

key priority research questions by developing institutional capacity at diverse research sites. As described in Boxes 3-3 and 5-1, establishment of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network has benefited research on human immunodeficiency virus (HIV) treatment during pregnancy and lactation. Other research networks that NICHD supports contribute to research on various conditions experienced by pregnant and lactating women and involve collaborations with other NIH institutes and centers.

Collaboration through research networks comprising diverse populations and geographic sites promotes a greater effect and generalizability of scientific discoveries, innovative thinking, mentorship of early-career researchers, and the development of research capacity and sustained infrastructure (Disis and Slattery, 2010; Jones et al., 2008; Luke et al., 2016; Snowden et al., 2018). Mentorship and research capacity are particularly important factors to the safe inclusion of pregnant and lactating women in clinical research, therefore mitigating the potential for liability. Expansion of existing NIH networks for pregnancy and lactation research is necessary to accommodate the need and demand for highly qualified researchers and research institutions. Consideration of the ability of future network sites to recruit and retain diverse research participants is important to consider.

Recommendation 6. 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.**

A primary concern that has stalled the inclusion of pregnant and lactating women in clinical research is the fear that the research may cause harm in the research participant or in their fetus or infant (Frew et al., 2014). Notably, when harms occur among pregnant and lactating women, people of color and those of lower socioeconomic status lacking resources

to pursue a legal remedy are often left with no recourse and no compensation. There is no nationwide requirement or mechanism to compensate research participants who are harmed by their participation in a research study (Henry et al., 2015). The National Vaccine Injury Compensation Program (VICP), discussed in Chapter 4, provides compensation for injured individuals and incentivizes companies to develop and distribute vaccines by providing an alternate route for potential liability claims through a no-fault system (Winter et al., 2021). However, the VICP only covers certain vaccines recommended by CDC.

Although research institutions may have their own policies to compensate individuals with research-related injuries, it is not common practice (Resnik et al., 2014). Researchers and staff at a research university that undertakes research with pregnant women identified the availability of a university mechanism to compensate individuals for research-related injuries as an important contributor to the university's successful research portfolio in pregnant women (Mastroianni et al., 2020). Moreover, the university's compensation program may contribute to the low number of research-related lawsuits and tort claims faced by the university.

While the United States does not require the provision of no-fault compensation for research-related injuries, many other countries do (Pike, 2012). Given the shortcomings of the American tort system detailed in Chapter 2, it may be challenging for research participants who are harmed in clinical research to obtain any compensation. A clinical trial insurance plan purchased by an investigator, research institution, or sponsor could be a solution to provide modest compensation for research-related injuries. An insurance policy that covers no-fault compensation enables those harmed by participation in clinical research to receive compensation up to a certain limit for immediate medical expenses without resorting to the tort system (Medmarc, 2022).

Because acquiring clinical trial insurance imposes an additional cost to the study, it would be appropriate for NIH to cover the cost of clinical trial insurance for NIH-funded research involving pregnant and lactating women, which is within its authority (Henry et al., 2015). While the cost of policies for studies including pregnant and lactating women may be expensive at first, owing to scant actuarial data for these populations, the committee finds that the cost of coverage is likely to moderate over time as the uncertainty of insurance underwriters decreases. Moreover, clinical trial insurance would incentivize sponsors and investigators to minimize harm as the price of an insurance policy is likely to decrease if proper safeguards are in place and the investigator and research institution can demonstrate a consistent record of safety (Pike, 2012).

Recommendation 7. 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.

IMPROVE EXISTING DATA AND SAFETY MONITORING

Given the exclusion of pregnant women from clinical trials, most of the in-human safety data related to the use of products by pregnant and lactating women are now generated through postmarketing observational studies (Roque Pereira et al., 2022; Stock and Norman, 2019). Conducting more clinical trials with pregnant and lactating women will not lessen the need to expand the collection and analysis of real-world data to enrich the basic safety and efficacy profile built through clinical trials. Real-world data collected through observational studies are important for detecting rare adverse events and understanding the long-term safety profile of medical products, but 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.

FDA has developed draft guidance for industry on postapproval pregnancy safety studies, which provides considerations on the design, use, and analysis of pregnancy exposure registries and complementary databases (FDA, 2019), which is covered in Chapter 3. FDA has also pledged to make improvements to the collection of real-world safety data in pregnancy through the development of a framework and demonstration projects in its Prescription Drug User Fee Act (PDUFA) VII commitments (FDA, 2023). Internationally, Europe's ConcePTION project, funded through the Innovative Medicines Initiative (IMI), is working to enhance and expand capabilities in collecting and analyzing observational data (IMI, 2023). IMI ConcePTION's efforts include improving interoperability of data systems, defining core data elements, constructing workflows for data analysis, and optimizing data linkages between parents and offspring. While there are notable differences between the electronic health data infrastructure of European countries and the United States, many of the lessons from IMI ConcePTION may still be applicable as the United States aims to achieve similar goals.

Existing pregnancy exposure registries are often specific to a product or condition, requiring potential participants or their providers to search for relevant registries. 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 pregnant individuals, clinicians, and researchers with information regarding the safety of medical products in pregnancy and during breastfeeding. An important first step in designing such a repository would be to make it an interoperable, searchable resource for clinicians, investigators, or potential participants.

Sponsors conducting pregnancy exposure registries as part of a postmarketing commitment must submit annual status reports to FDA, and registries not conducted under postmarketing commitments are still encouraged to submit such reports (FDA, 2002). Ideally, the repository would be constructed to capture data submitted through these annual status reports. The usefulness of a repository would be greatly increased if it also included summary information from postmarketing adverse event reports that are required to be submitted to FDA.[9,10] While some of these adverse event data are likely to be captured by the FDA Adverse Event Reporting System (FAERS) and Vaccine Adverse Event Report System (VAERS), collecting such information in a single repository focused on pregnancy and lactation would likely improve accessibility for pregnant and lactating women and their health care providers. The repository would benefit from being designed with end users in mind. For example, the repository could have prepopulated submission categories with information requested in FDA's "Guidance for Industry on Establishing Pregnancy Exposure Registries," and dropdown menu selections, where relevant. Additionally, nonproprietary information in the status report for each registry that would be useful to be made public in the repository includes:

- Number of pregnant women enrolled to date,
- Number of pregnancies with unknown outcomes,
- Number of pregnancies with outcome pending,
- Number of pregnancies lost to follow-up, and
- Number and type of adverse events reported.

Unlike pregnancy, there are very few lactation registries that exist worldwide. A few product-specific registries exist; however, there is no

[9] *Postmarketing reporting of adverse drug experiences.*, 21 CFR 314.80.
[10] *Postmarketing reporting of adverse experiences.*, 21 CFR 600.80.

comprehensive prospective lactation registry. Such a prospective lactation registry, collecting data on maternal medication consumption and adverse events in the child, would be a critical data repository to increase the information on medication safety during lactation. The LactMed database administered by NICHD collects published data on medications and chemicals to which lactating mothers may be exposed, with information on human milk transfer, and concentrations and adverse events in the nursing child (NIH, 2023a).

Most postapproval programs for lactation are focused on developing biobank capacity and preclinical modeling. This is likely because lactation studies generally require the collection of human milk to determine how much of a medication the child is exposed to, which makes the lactation studies interventional and not observational (Covington, 2018). To collect more data on medication use during lactation, NICHD is funding a multicenter study focused on conducting population-based PK studies during lactation for a variety of already approved medications that the lactating parent is already receiving for therapeutic reasons (Pediatric Trials Network, 2023).

The electronic health data that are used to conduct complementary database studies are fragmented across different platforms and health care systems (Reisman, 2017; Turbow et al., 2021). Such fragmentation makes it difficult to share data and to construct large datasets that would enable more robust analyses with greater statistical power. Another challenge is a lack of common data elements that are important to capture relevant to the safety of medical products for pregnant individuals and their fetuses (Richardson et al., 2023). For example, health records often do not collect information about breastfeeding practices, complicating research into the outcomes for breastfeeding children given the inability to determine exposure.[11] A lack of data linkage between the pregnant individual and their offspring is another barrier to conducting database studies in pregnant women (Whitmore et al., 2021).

The linkage of parental and offspring electronic health records is vital to understanding fetal and infant outcomes related to exposure to medical products in utero. Yet, creation of these linkages is a challenge for real-world data studies conducted in the United States and may be particularly difficult when using Medicaid data (Johnson et al., 2013). FDA's Sentinel Initiative added mother–child linkages to its database in 2018, beginning originally with data from private insurers and expanding to include Medicaid data in the last few years. Of the live births in their database, approximately 80 percent have mother–child linkages (Maro, 2023).

[11] As presented to the committee by Christina Chambers in open session on June 15, 2023.

Further attention to addressing these limitations may improve the feasibility of conducting real-world data studies with pregnant and lactating women.

Recommendation 8. 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. From within its membership, the task force should identify agency leads to carry out the following activities:

a. **Develop a central repository to collect postmarketing safety data from pregnancy and lactation exposure registries and database studies.**
b. **Release guidelines on the content and format of data to be submitted to the central repository from existing pregnancy and lactation exposure registries, which should include, at a minimum, the following: number of pregnant and lactating women enrolled to date, number of pregnant and lactating women with unknown outcomes, number of pregnant and lactating women with pending outcomes, number of pregnant and lactating women lost to follow-up, and number and types of adverse events reported in pregnant and lactating women.**
c. **Adopt standards requiring that the electronic health records of pregnant and lactating women be capable of being linked with records for their offspring in research databases.**
d. **Evaluate the infrastructure, data elements, and resources that would be required to develop and maintain a centralized national registry for collecting and evaluating postmarketing data from pregnant and lactating women.**

PROTECT RESEARCH PARTICIPANTS' PRIVACY

The committee's review of litigation did not reveal any legal liability exposure related to an injured child's claim based on a parents' participation in clinical research while the child was in utero. Many states have

some level of parent–child immunity. There are a few atypical cases, however, that have recognized a potential claim by a child against a mother whose negligence caused damages in utero (Clayton, 1994), one of which is a case against a mother who took medication while pregnant that claimed she failed to exercise "reasonable parental discretion."[12] A number of states also have broad child abuse statutes that might be interpreted to expose a mother to liability because of medications taken while pregnant. Following the U.S. Supreme Court decision in *Dobbs v. Jackson Women's Health Organization*, overturning its previous rulings that the U.S. Constitution protected the right to an abortion, research participants may be exposed to new legal liability depending on state laws and local enforcement. Charges of civil or criminal liability could be brought against research participants that experience a spontaneous abortion or seek an elective abortion. Furthermore, an individual's right to privacy is not necessarily "absolute; rather, it is a conditional right which may be infringed upon a showing of proper governmental interest."[13]

Certificates of Confidentiality

Certificates of confidentiality (CoCs) provide an opportunity to protect against the potential for legal liability, especially following the *Dobbs* decision, should the privacy of research participants be breached.

A CoC can help achieve the research objectives and promote participation in studies by safeguarding the confidentiality of subjects' information by protecting researchers and institutions from being compelled to disclose information that would identify research subjects. CoCs help reassure participants that their data are safe and protected from disclosure or use in legal proceedings. Such protection may be particularly necessary in states with laws that could criminalize or hold liable a pregnant individual should their fetus be harmed in the course of clinical research.

Recommendation 9. 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.

[12] *Grodin v. Grodin*, 301 N.W.2d 869, (Mich. App. 1981).
[13] *Planned Parenthood of Southern Arizona v. Lawall*, 307 783 (9th Circuit 2002).

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A

Public Meeting Agendas

Meeting 1 Agenda Thursday, January 26, 2023	
10:30–11:30 a.m.	**CLOSED SESSION—COMMITTEE MEMBERS ONLY**
11:30–11:50	*Break*
OPEN SESSION	
11:50–11:55	**Welcome and Introductions** Mimi Foster Riley, *Committee Chair* Professor of Law University of Virginia
11:55–12:10 p.m.	**Sponsor Perspective and Charge to the Committee** Camille Fabiyi Program Officer, NICHD National Institutes of Health Aaron Pawlyk Chief, Obstetric and Pediatric Pharmacology and Therapeutics Branch, NICHD National Institutes of Health

Nahida Chakhtoura
Branch Chief, Pregnancy and
Perinatology Branch, NICHD
National Institutes of Health

12:10–12:45 **Discussion with Committee**

12:45 **ADJOURN OPEN SESSION**

12:45–1:45 ***Break***

1:45–4:30 **CLOSED SESSION—COMMITTEE MEMBERS ONLY**

4:30 **END OF MEETING**

Meeting 2 Agenda
Thursday, March 23, 2023
CLOSED SESSION—COMMITTEE MEMBERS ONLY

9:30–10:00 a.m. **Closed Session Deliberations**

OPEN SESSION—PUBLIC WORKSHOP
Welcome and Introduction

10:00–10:10 **Opening Remarks**
Mimi Foster Riley, *Committee Chair*
Professor of Law
University of Virginia

SESSION I – product liability Considerations

Session Objectives

- Discuss the role of product liability considerations in creating incentives and/or disincentives for medical product companies to generate evidence for the safety and efficacy of their products in pregnant and lactating populations; and
- Consider what incentives and accountability measures may be effective in generating evidence for pregnant and lactating populations.

10:10–10:25 **Fireside Chat**
Bruce Kuhlik, *Moderator*
Former General Counsel
Merck & Co.
Defense Attorney Perspective

John Beisner
Partner
Skadden, Arps, Slate, Meagher &
Flom LLP and Affiliates

10:25–10:45 **Discussion with Committee**

SESSION I—THE ROLE OF RISK MANAGEMENT AND TRIAL INSURANCE

Session Objectives

- Understand what factors or considerations influence decisions to include or exclude pregnant and lactating populations from clinical research;
- Discuss how risk and benefit are assessed for populations that are being considered for inclusion in a clinical research study, as well as for the institutions conducting, funding, or insuring the study; and
- Examine opportunities to apply risk mitigation strategies to clinical research that includes pregnant and lactating populations.

10:45–11:10 **Panel Discussion**
Patricia Danzon, *Moderator*
Celia Moh Professor of Healthcare Management
University of Pennsylvania

Trial Insurance Perspective
Sara Dyson
Vice President of Underwriting Operations
and Risk Management
Medmarc

Academic Medical Center Perspective
Hillary Noll Kalay
Principal Counsel
University of California

Institutional Review Board Perspective
Elisa Hurley
Executive Director
Public Responsibility in Medicine and Research

11:10–11:45 **Discussion with Committee**

11:45–12:45 **LUNCH BREAK**

SESSION III—EQUITY CONSIDERATIONS FOR INJURY COMPENSATION

Session Objectives

- Understand how research participants view and make decisions regarding participation in clinical research while pregnant or lactating;
- Consider various perspectives on what constitutes fair and just compensation for participants harmed in the course of clinical research;
- Examine the benefits and drawbacks to different injury compensation schemes in the context of promoting fairness and justice; and
- Discuss opportunities to improve upon existing compensation schemes to make them more equitable.

12:45–1:00 **Presentation**
Jason Malone
Director of the Human Subjects Division
University of Washington

1:00–1:45 **Panel Discussion**
Anne CC Lee, *Moderator*
Director of Global Newborn Health
Brigham and Women's Hospital
Harvard Medical School

Research Participant Perspective
Yvette Raphael
Executive Director
Advocacy for Prevention of HIV and AIDS
in South Africa

Marcela Smid
Research Participant
Jillian Brown
Research Participant

No Fault Compensation Perspective
Efthimios Parasidis
Chief Justice Thomas J. Moyer Professorship for the Administration of Justice and Rule of Law
Ohio State University

Renée Gentry
Principal Partner
The Law Office of Renée J. Gentry

Tort Perspective
Michelle Mello
Professor of Law and Health Policy
Stanford University

1:45–2:30 **Discussion with Committee**

2:30–3:00 **BREAK**

SESSION IV—CASE STUDIES IN RISK MITIGATION

Session Objectives

- Consider approaches that various institutions have adopted to mitigate risk and liability in clinical research that includes pregnant or lactating persons;
- Discuss challenges and successes of adopting and implementing risk and liability mitigation strategies for research involving pregnant or lactating persons; and
- Discuss opportunities to scale risk and liability mitigation strategies to other clinical research studies that could include pregnant or lactating persons.

3:00–3:20 **Panel Discussion**
Anna Mastroianni, *Moderator*
Research Professor
Johns Hopkins University

Nonprofit Perspective
Metin Gülmezoglu
Executive Director
Concept Foundation

Niranjan Bhat
Senior Medical Officer
PATH

Industry Perspective
Lorien Urban
Senior Medical Director, Clinical Development
Ferring Pharmaceuticals

3:20–4:00 **Discussion with Committee**

WORKSHOP ADJOURNS
CLOSED SESSION—COMMITTEE MEMBERS ONLY

4:15–4:30 **Closed Session Deliberations**

4:30 **ADJOURN DAY 1**

Friday, March 24, 2023
CLOSED SESSION—COMMITTEE MEMBERS ONLY

9:30–4:00 **Closed Session Deliberations**

Meeting 3 Agenda
Thursday, June 15, 2023
CLOSED SESSION—COMMITTEE MEMBERS ONLY

OPEN SESSION

10:15–11:15 **Real-World Data and Real-World Evidence: Challenges and Opportunities Panel Discussion**
Ahizechukwu Eke, *Moderator*
Director of Research, Division of
Maternal-Fetal Medicine
Johns Hopkins University

Industry Registry Perspective
Kristin Veley
Executive Director, Research Science
Epidemiology and Scientific Affairs, PPAS & RWE
PPD

Human Milk Biorepositories Perspective
Tina Chambers
Professor of Pediatrics
University of California San Diego

FDA Perspective
Tamara Johnson
Lead Medical Officer
Division of Pediatric and Maternal Health
FDA

Clinical Researcher Perspective
Jonathan Watanabe
Associate Dean of Pharmacy Assessment and Quality
University of California Irvine

11:15–11:30 **Coffee Break**

11:30–12:15 **Discussion: Liability for Pregnant and Lactating Persons Exclusion**
Leslie Meltzer-Henry, *Moderator*
Professor of Law
University of Maryland

Alan C. Milstein
Shareholder & Chairman, Department of Litigation
Sherman, Silverstein, Kohl, Rose & Podolsky, P.A.

12:15–1:15 **LUNCH BREAK**

1:15–2:15 **Presentation on FDA Commissioned Paper**
Julie Tibbets
Partner
Goodwin Procter LLP

Sarah Wicks
Associate
Goodwin Procter LLP

2:15–2:30 **BREAK**

	CLOSED SESSION—COMMITTEE MEMBERS ONLY
2:30–4:30	**Closed Session Deliberations**
4:30	**ADJOURN DAY 1**
	Friday, June 16, 2023 **CLOSED SESSION—COMMITTEE MEMBERS ONLY**
	OPEN SESSION
11:30–12:00	**Product Liability Discussion** Bruce Kuhlik, *Moderator* Former General Counsel Merck & Co. Kirke Weaver General Counsel Organon
	CLOSED SESSION—COMMITTEE MEMBERS ONLY
12:45–4:00	**Closed Session Deliberations**
4:00	**ADJOURN DAY 1**
	Meeting 4 Agenda **Thursday, July 13, 2023**
10:30–3:00	**CLOSED SESSION—COMMITTEE MEMBERS ONLY**
12:15–1:00	**Lunch Break**
	Friday, July 14, 2023
10:00–3:00	**CLOSED SESSION—COMMITTEE MEMBERS ONLY**
12:00–1:00	**Lunch Break**

Meeting 5 Agenda
Wednesday, September 27, 2023

10:30–1:00 **CLOSED SESSION—COMMITTEE MEMBERS ONLY**

OPEN SESSION

1:00–2:00 **Drug Development Incentive Programs: Experience with BPCA & PREA**

FDA Perspective
Prabha Viswanathan
Deputy Director
Office of Pediatric Therapeutics,
Officer of the Commissioner, FDA

NIH Perspective
Perdita Taylor-Zapata
Program Lead, BPCA Clinical Program
NICHD

Public Policy Perspective
Florence Bourgeois
Codirector, Harvard–MIT Center for Regulatory Science
Associate Professor of Pediatrics and Emergency Medicine
Harvard Medical School

2:00–2:15 **Coffee Break**

2:15–5:00 **CLOSED SESSION—COMMITTEE MEMBERS ONLY**

Thursday, September 28, 2023

10:00–3:00 **CLOSED SESSION—COMMITTEE MEMBERS ONLY**

Meeting 6 Agenda
Friday, October 20, 2023

10:00–5:00 **CLOSED SESSION—COMMITTEE MEMBERS ONLY**

B

Scope of Liability Related to Pharmaceuticals Dispensed to Pregnant and Lactating Women

AUTHORS

Lauren Colton, Phil Katz, Katherine Kramer, and Megan Dorsch,
Hogan Lovells US LLP, Consultants to the Committee, 2024

INTRODUCTION

The National Academies of Science, Engineering, and Medicine (NASEM) requested assistance with research regarding the potential scope of legal liability associated with drugs, biologics, or related medical devices prescribed to pregnant or lactating women. NASEM also asked that we identify, where applicable, any insights, patterns, or conclusions this legal landscape reveals, particularly with respect to the question of "What is the true legal risk associated with pharmaceutical products researched in, and dispensed to, pregnant and lactating women?"

RESEARCH METHOD

To address this research question, we consulted a variety of sources, including but not limited to legal research websites (e.g., Westlaw, Lexis), secondary sources (e.g., peer-reviewed literature, law review articles), and Internet sources to gather relevant case law. We did not limit our search to product liability actions but tailored our search terms to gather all potential case law related to drugs studied in or used by pregnant or lactating populations. We did not gather cases that did not have a publicly available court opinion. When the case law indicated substantial litigation surrounding a particular pharmaceutical product, we broadened our search basis in an effort to appraise the true breadth of litigation. For example, Internet, dockets, and secondary

sources may reveal the existence of settlements, the formation of multidistrict litigation (MDLs), and other legal activity surrounding a particular pharmaceutical product that the reported case law does not identify.[1]

We then prepared tables to consolidate and synthesize the case law and other relevant legal liability information we identified on this topic. The "Legal Landscape Overview" is appended to this memorandum as "Appendix A." The charts are divided by subtopic: (1) case law involving drugs used in lactating women; (2) case law involving drugs used "on-label" in pregnant women; (3) case law involving drugs used "off-label" in pregnant women; and (4) case law specifically involving medical malpractice claims. Each chart provides the case name (Case), relevant pharmaceutical product (Drug), a brief description of whether the labeling included any warnings or a contraindication for use in pregnant or lactating populations, to the extent this information is available (Labeling information), the type of plaintiff and specific injury alleged (Plaintiff/injury), the claims asserted by the lawsuit (Claims), a description of the case disposition and relevant holdings (Case description), and a Settlement/Verdict amount, if applicable. When there were a vast number of cases regarding a particular drug or area of liability, we provided a high-level summary of the litigation and a representative subset of cases (e.g., "DES Cases" and "Accutane Cases").

[1] We also collected a sample of lawsuits filed during the last year (Aug. 2022–2023). A senior research analyst pulled complaints from *Courthouse News* and *Bloomberg Law* using the following search terms:

- CN: (drug OR pharma! OR biologic! OR device) AND (pre-natal OR prenatal OR post-natal OR postnatal OR pregnancy OR pregnant OR breastfeeding OR "breast feeding" OR miscar!)
- BL: (pregnant OR pregnancy OR lactat! OR breastfeed! OR pre-natal OR post-natal OR post-partum OR postpartum OR miscar!) w/8 (drug OR pharma! OR biologic! OR device).

A review of the complaints for this time period revealed that the majority of recently filed lawsuits involved either DES or acetaminophen. We did not include these new lawsuits in our summary materials, for several reasons, including: (1) these lawsuits reflect patterns and redundancies already seen in the existing, reported case law; (2) reviewing and summarizing these materials, beyond confirming that they involved personal injury claims related to DES and acetaminophen, was not likely to lead to a new or different conclusion in our liability analysis; (3) given the abundance of *reported* case law on this topic, we felt it was a better use of our resources to analyze existing precedent rather than cases that are in the very early stages of litigation.

The breadth of the research topic and the nature of product liability litigation do not lend themselves to certainty; we cannot warrant that we have identified *all* relevant cases or have a complete understanding of the legal landscape, particularly as it relates to unpublicized, undisclosed settlements. However, our findings did allow us to draw several conclusions regarding the legal risks and potential liabilities associated with pharmaceutical products used in pregnant and lactating populations as well as certain liability trends in this area (e.g., defenses, barriers to liability, the potential for long-tail liability or MDLs). Those conclusions are described in more detail below in Section C.

RESEARCH FINDINGS

Clinical Trial Liability

There is a dearth of case law in the clinical trial context related to pregnant and lactating populations. We were unable to find any reported case law in which a pregnant or lactating woman—or their children/grandchildren—filed suit against a drug manufacturer/designer, clinical trial sponsor, or any other entity for personal injuries related to their participation in a clinical trial or study.[2] Fear of liability is a regularly cited obstacle to the inclusion of pregnant women in clinical research,[3] yet the case law (or the lack thereof) does not evidence a materially greater risk of liability with respect to pregnant/lactating women as compared to other participants in clinical trials, such as children—a

[2] For completeness, we note that there are a few cases involving a medical experiment conducted by the University of Chicago and Eli Lilly & Company to determine the value of DES in preventing miscarriages. *See Mink v. Univ. of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978); *Wetherill v. Univ. of Chicago*, 570 F. Supp. 1124 (N.D. Ill 1983). DES was administered to over 1,000 pregnant women without their knowledge of the drug or consent to participate in the study. In *Mink*, the plaintiffs brought suit against the university and the manufacturer seeking recovery on theories of battery, products liability, and breach of duty to notify plaintiffs that they had been given drug (medical malpractice). Although the court denied the defendants' motion for summary judgment on the battery claim, the court granted the motion as to the plaintiffs' other claims because no personal injury was alleged.

Additionally, we identified a qui tam suit, brought under the False Claims Act, against clinical trial sponsor of COVID-19 vaccine for administering the vaccine/placebo to pregnant women in violation of the clinical trial protocol. No injuries were alleged. *See* Appendix A, *United States ex rel. Jackson v. Ventavia Research Group, LLC*, No. 1:21-CV-00008, 2023 WL 2744394 (E.D. Tex. Mar. 31, 2023) (appeal pending).

[3] Anna C. Mastroianni et al., *Research with Pregnant Women: New Insights on Legal Decision-Making*, 47 Hastings Ctr. Rep. 38 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5533594/ (author's manuscript at 7).

similarly sympathetic population.[4] Indeed, the tort system poses unique challenges to all research participants because they must show that they did not "assume the risk" through the informed consent process.[5] Further, "injured research participants are also often injured by unforeseen risks that are not anyone's fault and so fall outside the tort system entirely."[6]

Thus, scholars posit that the fear of liability is fueled in part by uncertainty. The "paucity of relevant and easily accessible precedents of approved research with pregnant women that might serve as a guide through regulatory pathways" means that the legal decision makers advising clients at each stage of the development process "have scant knowledge of what others in the same or similar position are doing."[7] Moreover, regulatory ambiguities surrounding Subpart B of the Department of Health and Human Services regulations,[8] including how the regulatory definition of "minimal risk" should be interpreted, whether "minimal risk" applies equally to all phases of pregnancy, and regulatory inconsistencies regarding the biological father's role in the informed consent process also factor into legal considerations that may result in the exclusion of pregnant women from clinical research.[9]

Despite the lack of legal precedent in this area, several potential claims *may* arise if a study participant (mother/lactating woman) and/or her child is injured as a result of clinical trial conduct. Based on our experience and expertise, potential claims are most likely to be asserted against the drug manufacturer and/or clinical trial sponsor and often include strict liability, negligence, and/or inadequate informed consent.[10]

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[4] The absence of case law may also reflect, to some extent, differences in the compensation systems for injuries resulting from clinical trials and FDA-approved products. Although U.S. laws do not require research sponsors or institutes to compensate human research subjects who experience a research-related injury, some institutions and research sponsors may agree to cover medical expenses if a research related injury occurs. *See* 21 C.F.R. § 50.25(a)(6) & 45 C.F.R. § 46.116 (requiring an explanation of whether compensation for research-related injuries is available for studies involving more than minimal risk). One study, albeit somewhat dated, estimated that about one half of research participants enrolled in research at medical schools have their medical bills for research-related injuries covered. Michael K. Paasche-Orlow & Frederick L. Brancata, *Assessment of Medical School Institutional Review Board Policies Regarding Compensation of Subjects for Research-Related Injury*, 118 AM. J. MED. 175, 177 (2005).

[5] Elizabeth R. Pike, *Recovering from Research: A No-Fault Proposal to Compensate Injured Research Participants*, 38 Am. J.L. & Med. 7, 23–24 (2012).

[6] *Id*. at 24.

[7] Mastroianni et al., *supra* note 3, at 7 (author's manuscript).

[8] Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research, 45 C.F.R. §§ 46.201–46.207 (2001).

[9] Mastroianni et al., *supra* note 3, at 5-7 (author's manuscript).

[10] Original authors provided a court transcript.

Generally, clinical trial claims tend to be based on the allegations that the participant was not adequately warned of the risks associated with the experimental product, was not an appropriate candidate for the study, or that the study was not designed appropriately.[11] Breach of contract claims are also often asserted based on the compensation provision of informed consent documents. Employing risk mitigation measures throughout the clinical trial process, such as instituting a robust and comprehensive informed consent process and ensuring that safety and efficacy are demonstrated in preclinical and animal studies before instituting research in human populations, can mitigate the risk of litigation. Examples of mitigation strategies include:

- Include clear statements in the informed consent regarding the known risks and the potential for unknown risks to assist with the defense to lack of informed consent cases and to support the assumption of risk defense. Also, consistent with FDA regulations, the consent document should be updated regularly as new safety information is obtained about the investigational product.
- Ensure that the Investigator's Brochure documents the known and potential risks associated with the investigational product to support the learned intermediary defense to a litigation claim.
- State in the clinical trial agreement with the investigator and in the informed consent document that the investigator is not an agent of the sponsor to preserves the sponsor's defense to a claim for lack of informed consent, which is consistent with the regulatory framework requiring the investigator to obtain consent. Such a statement may also support the defense to a negligence claim that the sponsor owed no duty to the study participant.
- State in the informed consent that the investigational product will be provided only during the course of the study, that there is no commitment to provide the investigation product after the study has concluded and that the sponsor may stop the trial at any time for any reason to protect against expanded access claims.
- State in the informed consent that the investigational product is being provided during the study free of charge and is not otherwise available to the study participant in the stream of commerce to provide documentary evidence to support the defense to a strict liability that such a cause of action is not appropriate for a product that is not in the stream of commerce.

[11] Clinical trial precedent—outside the of the pregnancy/lactation space—includes a line of "expanded access" cases involving claims for continued access to an experimental treatment after the study has ended. We have not detailed those cases here but are willing to provide additional information if those cases are of interest.

- State in the informed consent that the document is not a contract between the sponsor and the study participant to protect against breach of contract claims.
- Define clearly the definition of the medical expenses for which the sponsor will be responsible in the event of an injury and make clear that the injury must be directly related to the administration of the investigational product to preserve the lack of causation defense.

Lactating Women—Post Market Liabilities

We identified a number of personal injury lawsuits brought against drug manufacturers for injuries experienced by lactating women. However, the cases all related to the same drug: Parlodel, a lactation inhibitor,[12] and the injuries alleged (e.g., stroke and seizure) were suffered by the lactating woman ingesting the drug (see Table B-1). We did not identify any cases alleging an injury to a child caused by consumption of a drug present in breast milk.

The Parlodel litigation is notable for two related reasons. First, the cases demonstrate differing applications of the evidentiary standard for the admissibility of expert testimony set forth in the Supreme Court's landmark *Daubert* decision.[13] Consistent with our broader observations, cases where the court denied the manufacturer's dispositive motion were more likely to settle. Therefore, such jurisdictional differences—where courts in different jurisdictions apply the *Daubert* standard inconsistently—can make it harder for sponsors to predict the risk of liability. Second, and relatedly, the litigation sheds light on the potential legal effect of adverse administrative actions. In the years leading up to the Parlodel litigation, serious adverse event reports caused FDA first to encourage manufacturers to include a warning in their labeling and alert doctors to the potential hazards of using the drug for lactation suppression, and later, to initiate withdrawal proceedings for this indication for Parlodel based on the agency's conclusion that the possible risks outweighed the utility

[12] The following search terms were used to collect case law and secondary sources from Westlaw: "breastfeeding" or "lactation/ing", "drug," and "malpractice," "clinical trial," "liability," or "consumer protection." Based on these searches and supplemental internet searches, the only litigation identified with respect to lactating persons involved the drug Parlodel.

[13] Many cases were decided in Sandoz's favor on summary judgment motions on the basis that testimony offered by plaintiffs' expert witnesses lacked critical indicia of scientific reliability as set forth in the Supreme Court's *Daubert* to establish causation. See Stephen Otero & Melissa Roberts Levin, *"JAWS" Attacks On The Daubert Trilogy: A Case Study: The Parlodel® Litigation*, Troutman Sanders LLP, https://www.troutman.com/a/web/257/art-otero-levin2.pdf for a comprehensive summary of the Parlodel litigation.

of the drug in lactating women.[14] In declining to admit expert testimony based in part on FDA's risk-benefit determination, a number of courts noted that the FDA's risk-utility standard is lower than the standard of proof required in tort actions.[15] On the other hand, a minority of courts found the determination to be a reliable source of evidence.[16]

Pregnant Women—Post Market Liabilities

We found copious case law associated with pregnant women's use of pharmaceutical products, both on- and off-label, during various phases of their pregnancy (see Tables B-2,B-3). We refer to these cases as "post-market" liabilities herein because the pharmaceutical product was ingested after it was on the market versus during the clinical study phase of its development. These post-market cases involve pharmaceutical products prescribed for pregnancy-related conditions (e.g., Zofran—morning sickness) and for general ailments nonspecific to pregnancy (e.g., Zoloft—antidepressant). The overwhelming majority of these cases share the following characteristics:

- Personal injury lawsuits;
- Filed against the drug manufacturer or other entity involved in the chain of distribution (e.g., hospital and pharmacy);[17]
- The pregnant woman ingested the drug *in utero*, and the drug subsequently caused injury to the woman's child;
- The injury alleged is a birth defect, of varying types;
- The plaintiffs consist of either the child, the mother, or both individuals; and
- Common causes of action include violation of state consumer protection law, negligence, breach of warranty, failure to warn, fraud and strict liability.

And, as demonstrated by the below sub-sections of this Memorandum, the majority of the case law involving a pregnant woman's post-market

[14] *See* 60 F.R. 3403 (Jan. 17, 1995). Note that Parlodel is an FDA-approved drug doctors still prescribe today for multiple other uses.

[15] *See, e.g., Siharath v. Sandoz Pharmaceuticals Corp.*, 131 F. Supp.2d 1347, 1366 (N.D. Ga. 2001); *Glastetter v. Novartis Pharmaceuticals Corp.*, 107 F. Supp.2d 1015 (E.D. Mo. 2000), *aff'd* 252 F.3d 986, 990-91 (8th Cir. (per curiam), *petition for reh'g and reh'g en banc denied* (8th Cir. 2001).

[16] *See, e.g., Brasher v. Sandoz Pharma. Corp.*, 160 F. Supp. 2d 1291 (N.D. Ala. 2001) (medical causation); *see also Brasher v. Sandoz Pharma. Corp.*, 2001 WL 36403362 (N.D. Ala. Sept. 21, 2021) (denying summary judgment motion); *Globetti v. Sandoz Pharma. Corp.*, 111 F. Supp. 2d 1174 (N.D. Ala 2000) (holding the same on the issue of medical causation).

[17] The viability of claims against entities other than manufacturers is fact-specific and certain entities, such as pharmacies, may have only a limited duty to patients. *See Moore ex rel. Moore v. Memorial Hosp. of Gulfport*, 825 So.2d 658 (Miss. 2002); *see also infra* note 29.

ingestion of a pharmaceutical product can be categorized as: (1) product liability claims, or (2) medical malpractice claims.

1. *Products liability and related claims*.[18] As demonstrated by Tables B-2 and B-3, defendant-manufacturers are often successful in dismissing personal injury claims by filing dispositive legal motions (e.g., motions to dismiss or motions for summary judgment) on theories of preemption or lack of medical causation (*Daubert* motions).[19] As to preemption, defendants have successfully argued that manufacturers lack the ability to add certain warning to an approved product label, where there is insufficient evidence to trigger a manufacturer's ability to add plaintiff's desired warning, or where sufficient evidence is available, FDA considered all available safety information associated with the drug at the time of the injury and clear evidence shows that FDA would not have permitted the plaintiff's desired warning.[20] In such cases, courts have found warning contained in the product labeling to be adequate, as a matter of law.[21] On the other hand, where new evidence or analyses indicate that the manufacturer knew or should have known of an increased risk of injury that warranted a stronger warning under FDA's Changes Being Effected

[18] Cases were collected using various combinations of advanced search terms on Westlaw (e.g., "pregnan!" AND "drug" OR "pharm!"). Using broad searches, we then filtered the cases by case type to extricate products liability suits from the results. We also reviewed secondary sources.

[19] Although less common, several cases were also dismissed and/or judgment was granted in favor of the defendant, based on the learned intermediary doctrine. In these cases, the defendant would argue that the manufacturer had fulfilled its duty of care when it provides all necessary information to the prescribing physician, who is ultimately responsible for informing the patient of the risks and benefits associated with use of the drug. *See, e.g., Martin by Martin v. Ortho Pharmaceuticals*, 661 N.E.2d 352 (Ill. 1996); *Hunt by Hunt v. Hoffman-La Roche, Inc.*, 785 F. Supp. 547 (D. Md. 1992) (granting defendant's motion for summary judgment under learned intermediary doctrine, concluding that manufacturer warned prescribing doctor of risks associated with Accutane); *see also Moore ex rel. Moore v. Memorial Hosp. of Gulfport*, 825 So.2d 658 (Miss. 2002) (granting motion for summary judgment and extending the learned intermediary doctrine to the pharmacy).

[20] *See, e.g., In re Zofran (Ondansetron) Products Liab. Litig.*, 541 F. Supp. 3d 164 (D. Mass. 2021), *aff'd by In re Zofran (Ondansetron) Products Liab. Litig.*, 57 F.4th 327 (1st Cir. 2023). For a more thorough discussion of how courts have applied FDA preemption doctrine following the Supreme Court's decision in *Merck v. Albrecht*, 139 S. Ct. 1668, 1672 (2019), see generally Jamie Kendall et al., *FDA Preemptions and Albrecht's Progeny*, 76 FOOD & DRUG L.J. 579 (2022). The paper analyzes many of the birth defects-related cases cited in this analysis and Appendix A.

[21] *See, e.g., Zamfirova v. AMAG Pharmaceuticals, Inc.*, 2021 WL 2103287 (D.N.J. May 25, 2021), *Clark v. Hoffman-La Roche, Inc.*, 2006 WL 1374516 (Super. Ct. N.J. May 2, 2006), Willis v. Abbott Laboratories, 2017 WL 5988215 (W.D. Ky. 2017).

regulations,[22] courts have rejected dispositive motions.[23] Defendants are also successful in dismissing claims where plaintiffs' expert witnesses could not identify sufficiently reliable evidence to support causation—i.e., proof that the drug can actually cause the injury alleged (general causation) or did cause the alleged injury in that particular case (specific causation).[24] The success of both defenses often hinges on the scientific evidence before the Court—the existence of robust data demonstrating the safety/efficacy of the drug, data to support the adequacy of the warnings on the label, and/or the absence of data supporting a link between the drug and the injury alleged[25] can be determinative. The fact that science is critical to the defense of these claims is not surprising.

2. *Medical malpractice claims*.[26] Fewer reported cases involved claims asserted against practitioners. Some cases were brought against practitioners individually,[27] though, we identified a number examples where claims were asserted against the drug

[22] 21 C.F.R. § 314.70(c)(6)(iii)(A).

[23] *See, e.g., Kiker v. SmithKline Beecham Corp.*, 2026 WL 8189286 (S.D. Ohio Dec. 15, 2016); *Anderson v. Janssen Pharmaceuticals, Inc.*, No. 2330 EDA 2014, 2016 WL 2909234 (Pa. Super. Ct. May 11, 2016)

[24] *See, e.g., Zamfirova v. AMAG Pharmaceuticals, Inc.*, 2021 WL 2103287 (D.N.J. May 25, 2021), *Clark v. Hoffman-La Roche, Inc.*, 2006 WL 1374516 (Super. Ct. N.J. May 2, 2006); *Willis v. Abbott Laboratories*, 2017 WL 5988215 (W.D. Ky. 2017).

[25] Lawsuits involving pregnant women's ingestion of Accutane (*see* Appendix A, Table 2, pp. 12-13), demonstrate that the defendant can prevail in these lawsuits even if there is data *supporting* a link between the drug and injury alleged. In fact, general causation (evidence that Accutane can cause the injury alleged) is often a foregone conclusion in these lawsuits because Accutane's teratogenic effects were well-documented when the drug received FDA approval. The Accutane label included a black-box warning disclosing the high risk of birth defects since 1984. Therefore, courts frequently ruled in favor of the defendant-manufacturer in Accutane birth defect suits because the warnings were deemed "adequate" as a matter of law.

Similarly, the court may rule on a dispositive motion where the injury alleged is not of the same type known to be associated with a drug.

[26] Cases were collected using advanced search terms (+"medical malpractice" AND +"birth defect" (or) +"pregnancy" AND +"drug" (as well as specific drugs commonly involved in litigation, *e.g.*, Accutane) and reviewing secondary sources.

[27] *See, e.g., Dyson v. Winfield*, 113 F. Supp. 2d 35 (D.D.C. 2000), *judgment aff'd*, 21 Fed. Appx. 2 (D.C. Cir. 2001) (case against manufacturer); *Dyson v. Winfield*, 2d 44 (D.D.C. 2000) (case against practitioner); *Hunt by Hunt v. Hoffman-La Roche, Inc*. 785 F. Supp. 547 (D. Md. 1992) (discussing an earlier case brought against practitioners); *Muhammad v. Abbott Labs., Inc.*, 203 N.E.3d 1001 (Ill. App. Ct., 1st Dist., 4th Div. 2022) (discussing an earlier case brought against practitioners, where $18.5 million was awarded in damages). These examples may suggest that more cases are brought against practitioners than reflected in the case law.

manufacturer *and* practitioners as co-defendants.[28] Here, different claims were asserted against each defendant—i.e., products liability with respect to the manufacturer and negligence with respect to the practitioner.[29]

Of note, expert medical testimony is necessary to establish the physician's standard of care—that is, courts have not permitted plaintiffs to use a drug's prescribing information (and the *Physician's Desk Reference* [PDR]) to establish the standard of care. Warnings are generally admissible when accompanied by expert testimony, but the drug's labeling is not considered conclusive evidence of a violation of the standard of care.[30] To hold otherwise would undermine physician discretion to act in the patient's best interest, including by prescribing products off-label. Nevertheless, failure to provide warnings or to adhere to strict prescription guidelines may be strong evidence of a breach of the standard of care.[31]

Further, a common fact pattern in the medical malpractice cases we found involved physicians who failed to properly diagnose a plaintiff's pregnancy before prescribing a drug contraindicated for pregnant women and/or failed to warn the pregnant person of the risk of birth defects associated with a particular drug product.[32] Like in products liability cases, plaintiffs must establish medical causation in medical malpractice cases.[33] To that end, plaintiffs are much more likely to meet their burden of proof in such cases where it is well established that the drug ingested causes birth defects (e.g., Accutane, Provera).

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[28] *E.g., Ambrosini v. Labarraque*, 966 F.2d 1464 (D.C. Cir. 1992); *Vaccaro v. Squibb Corp.*, 418 N.E.2d 386 (N.Y. 1980) (bringing claims against manufacturer, physician, and hospital); Baker v. St. Agnes Hosp. 70 A.D.2d. 400 (N.Y. App. Div. 1979) (also asserting claims against manufacturer, Eli Lilly).

[29] It is worth mentioning that physicians (and hospitals) are unlikely to face strict product liability claims as retailers or other distributors. *See* Lars Noah, *This Is Your Products Liability Restatement on Drugs*, 74 Brooklyn L. Rev. 839 (2009).

[30] *See Spensieri v. Lasky*, 723 N.E.2d 231 (N.Y. Ct. App. 1999) ("[t]he purposes behind [drug labeling] render its content ill-suited to serve as prima facie evidence of a standard of care,")

[31] *See Hogle v. Hall By and Through Evans*, 916 P.2d 814 (Nev. 1996).

[32] *See, e.g., McClendon v. Williams*, 110 So.3d 216 (La. Ct. App., 2d. Cir., 2013), rev'd by *McClendon v. Williams*, 126 So.3d 1270 (La. 2013); *Hogle v. Hall By and Through Evans*, 916 P.2d 814 (Nev. 1996); *Lynch v. Bay Ridge Obstetrical & Gynecological Assoc.*, 532 N.E.2d 1239 (N.Y. Ct. App. 1988); *Hogle v. Hall By and Through Evans*, 916 P.2d 814 (Nev. 1996).

[33] *See, e.g., R.R. By and through Stowell v. Dandade*, 2017 WL 2117386 (N.M. Ct. App. Apr. 25, 2017) (excluding untested and unsupported medical testimony); *Davis v. United States*, 2015 WL 11142426 (N.D. Ga. Mar. 31, 2015) (rejecting plaintiff's "damaged sperm" theory); *Serigne v. Ivker*, 808 So.2d 783 (La. App. Ct., 4th Cir., 2002) (dismissing the case due to a lack of expert testimony on the issue of causation, despite evidence that the physician breached the standard of care by prescribing phenobarbital to a pregnant person).

Potential for Long-Tail Liability and Mass Litigation

The Legal Landscape Overview (Appendix B-1) evidences the Plaintiffs' Bar's clear preference for birth defect claims. The unborn child is a highly sympathetic plaintiff. Because certain harms can take years to manifest in the child—and the statute of limitations does not start to run until the child reaches the age of majority (i.e., often age 18, in many states)—this creates a longer window of time for plaintiffs to file suit against a culpable party. This is often referred to as "long-tail" liability. "A long-tail claim involves tortious or other liability-creating conduct that causes latent bodily injury or property damage that then manifests itself only many years after the harm-causing conduct occurred."[34] Long-tail claims often involve a massive number of claimants, in part because it is easier to spot a pattern emerging when there is a larger number of parties suffering the same kind of harm.[35] There are several notorious mass tort cases in which there was a long-tail between a pregnant woman's exposure to a drug and her child's manifestation of a birth defect. Those cases involve the drugs thalidomide, Bendectin, and diethylstilbestrol (DES), described briefly below:

- **Thalidomide:** Thalidomide was a morning sickness drug that entered the market in the 1950s in several foreign countries, including but not limited to Germany, the United Kingdom, Australia, Japan, Canada, and Norway. The drug was banned in most countries by 1961 when within just a few years of the drug being on the market approximately 10,000 children were born with phocomelia (a rare congenital birth defect that causes limb reduction anomalies).[36] Thalidomide-exposed children suffered a variety of injuries, including developmental disabilities, kidney malformations, and ocular anomalies, among others.[37] In 1961, two independent clinicians confirmed that thalidomide caused severe birth defects in children, and "[t]he evidence that thalidomide causes birth defects is now undoubted."[38] Fortunately, thalidomide was never FDA approved for use in pregnant women in the United States, and litigation in countries outside of the United States spanned decades.

[34] Kenneth S. Abraham, *The Long-Tail Liability Revolution: Creating the New World of Tort and Insurance Law*, 6 U. Penn. J.L. & Pub. Aff. 346, 348 (2021).

[35] *Id.* at 357.

[36] James Kim & Anthony Scialli, *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease*, 122 Toxicological Sciences 1, 1 (2011).

[37] *Id.* at 3.

[38] Neil Vargesson, Review, *Thalidomide-Induced Teratogenesis: History and Mechanisms*, 105 Wiley Birth Defects Rsch 141, 141–42. (2015).

- **Bendectin:** This FDA-approved morning sickness drug was prescribed to over 35 million American women between 1956 and 1983, before it was withdrawn from the market.[39] Concerns about a possible link between Bendectin and birth defects resulted in over 2,000 claimants filing suit against the manufacturer, Merrell Dow Pharmaceuticals.[40] In 1984, Merrell Dow offered to settle the majority of these claims (for $120 million) and ceased sales of Bendectin because the costs of litigation were too high. The court did not approve the settlement, and a trial was held for 818 Bendectin cases in federal court in Ohio. After hearing the evidence, the jury decided in favor of Merrell and found that plaintiffs failed to establish that Bendectin was a proximate cause of human birth defects.[41] Unlike thalidomide, no causal link between Bendectin and birth defects was ever scientifically established.[42] Possibly a testament to Bendectin's safety, in 2013, the FDA approved a rebranded version of Bendectin, Diclegis, for use in the treatment of "nausea and vomiting of pregnancy in women who do not respond to conservative management."[43] We were unable to find any reported litigation involving Diclegis, despite Bendectin's litigious history.
- **DES:** DES is a synthetic estrogen that was approved for treatment of miscarriage, preterm labor, and related pregnancy complications. It was widely prescribed to pregnant women between 1940 and 1971.[44] In 1971, an article in the *New England Journal of Medicine* reported a possible correlation between DES and clear cell adenocarcinoma of the vagina and cervix in girls and young women who were prenatally exposed to DES.[45] DES has been linked to a variety of reproductive cancers, fertility problems, and related medical conditions in woman that ingested DES, offspring of mothers that ingested DES in utero ("DES daughters"), and even

[39] Betsy J. Grey, Book Review, Michael D. Green, Bendectin and Birth Defects: The Challenges OF Mass Toxic Substances Litigation 83 (1996).

[40] *Id.*

[41] In *Re Richardson-Merrell, Inc. Bendectin Products Liability Litigation*, 624 F. Supp. 1212 (S.D. Ohio 1985); *see also* Richard Goldberg, *Scientific Evidence, Causation and the Law – Lessons of Bendectin (Debendox) Litigation*, 4 Med. L. Rev. 32 (1996).

[42] *Id.* at 36.

[43] Dicelegis, NDA Approval Letter, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/021876Orig1s000ltr.pdf.

[44] Nat'l Cancer Inst., *Diethylstilbestrol (DES) Exposure and Cancer*, https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet.

[45] National Academies of Sciences, Engineering, & Medicine, Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies, vol. 1, 238 (Anna Mastroianni et al. ed) (1994).

> third-generation populations.[46] It is estimated that several million pregnant women ingested DES over a 25-year period, resulting in an estimated 1,000+ individual or class-action products liability lawsuits against the pharmaceutical companies that manufactured DES.[47] The majority of the cases were filed in the 1980s/1990s, decades after the exposure. Yet, further demonstrative of the "long-tail" liability risk, new DES cases are still being filed *today*,[48] and plaintiffs' firms still advertise DES lawsuits on their websites.[49]

Other than DES, these litigations are not described or included in Appendix A because the swell of litigation occurred, and largely resolved, decades ago.[50] We included a sampling of DES cases in Appendix B-1 because DES litigation is ongoing to this day. And, as described in the Table, DES litigation demonstrates two "long-tail" liability themes: (1) the potential for litigation initiated by third-generation plaintiffs ("DES granddaughters" that experienced injuries from their grandmother's ingestion of DES in utero); and (2) the difficulty identifying a culpable defendant (the manufacturer responsible for supplying the drug that injured a particular plaintiff), where there are numerous defendants manufacturing the same drug over an extended period of time.[51]

Although the thalidomide, Bendectin, and DES cases are largely "cautionary" tales[52] in terms of liability, history has a tendency to repeat itself. For example, today, we still see "mass" litigations, particularly multidistrict litigations (MDLs), involving pharmaceutical products

[46] DES cases can be found at Appendix B-1

[47] *See* Women and Health Research, *supra* note 45, at 239.

[48] *See supra* note 1; *see, e.g., Lalor v. Eli Lilly & Co. Complaint*, 1:22cv6872 (E.D.N.Y. Nov. 10, 2022).

[49] *See, e.g.*, Napoli Shkolnik PLLC, DES Daughters And Serious Injury, https://www.napolilaw.com/practice-areas/diethylstilbestrol-des/.

[50] *See* Appendix A, pp. 10–12.

[51] WOMEN AND HEALTH RESEARCH, *supra* note 45, at 239

[52] Yet, there are several long-lasting positive impacts the thalidomide and Bendectin litigation had on drug safety and liability regimes. The thalidomide tragedy was said to "completely change[] the way drugs are tested." Vargesson, *supra* note 38, at 141. For example, thalidomide demonstrated that there are species differences in drug reactions, and today, drug screening policies now incorporate several species and in vitro tests. *Id*. at 142. Thalidomide also led to "universal" testing of all drugs for teratogenicity and resulted in more rigorous procedures for drug licensing. *See* Peter J Lachmann, *The penumbra of thalidomide, the litigation culture and the licensing of pharmaceuticals*, QJM: An International Journal of Medicine 105, no. 12 (2012): 1179-1189. Meanwhile, the Bendectin litigation resulted in the landmark case, *Daubert v. Merrell-Dow Pharmaceuticals Inc.*, which introduced a more rigorous standard for admitting scientific evidence based on the relevance and reliability of such evidence. *See* Goldberg, *supra* note 41, at 48-50. As demonstrated in Appendix A, numerous defendant-manufacturers have since prevailed on birth defect lawsuits involving pregnant women's ingestion of a pharmaceutical product, using the *Daubert* precedent.

ingested by pregnant women. An MDL is a type of civil procedure in the federal court system that is used when multiple lawsuits are pending against the same defendant or set of defendants and the lawsuits share common factual/legal issues. Appendix A demonstrates that there have been several recent MDLs involving birth defect injuries suffered as the result of a pregnant woman's ingestion of the following drugs: Depakote, Zofran, and Zoloft.[53] Over 700 of the Zofran and Zoloft MDL lawsuits were dismissed, and judgment was entered on behalf of the defendant manufacturers, on issues of preemption or general causation.[54] However, these defense "wins" in MDL cases come at a high cost to the drug manufacturer (i.e., time, money, resources, reputational burden), perhaps confirming that stakeholders' fear of liability in developing and marketing drugs towards pregnant women is not entirely unfounded.[55]

CONCLUSION

The legal landscape associated with pharmaceutical products researched in and dispensed to pregnant and lactating women reveals several key themes. Most notably, the case law does not corroborate stakeholders' fear that including pregnant or lactating women in clinical studies will result in significant litigation risk. At the very least, there is no indication that the legal risk of including pregnant or lactating women in clinical studies *exceeds* the risk drug manufacturers and clinical trial sponsors typically assume when conducting human trials on any pharmaceutical product.

In contrast, as revealed by our Legal Landscape Overview, there is no paucity of case law in the post-market space. The true legal risk associated with drugs dispensed to pregnant women is best assessed by reviewing this post-market case law. Product liability lawsuits, particularly birth defect claims, comprise the majority of the case law in Appendix A. Compared to pharmaceutical product liability litigation generally, products liability cases involving pregnant women reveal similar risks (e.g., latent injuries, potential for MDLs) and similar defenses (e.g., preemption and causation) that hinge on the drug's safety and efficacy data, the drug's labeling/warnings, and the scientific record before the Court. Although children injured in utero are particularly sympathetic plaintiffs and may present a more significant long-tail liability risk than other plaintiffs, the cases we found can, in many ways, be analogized to the pharmaceutical litigation landscape overall

[53] *See* Appendix B-1. Although it is outside the scope of the committee's domain, we also note that there is MDL in the Southern District of New York involving acetaminophen. *Id.* at 17-20.

[54] *See* Appendix B-1.

[55] Mastroianni et al., *supra* note 3, at 7 (author's manuscript).

APPENDIX B-1

TABLE B-1 Summary of Lawsuits Brought by Lactating/Breastfeeding Women[1]

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
			Parlodel			
Overview/Summary: In 1980, Parlodel® (bromocriptine) was approved for the prevention of postpartum lactation. Estimates suggest that 300,000 women who chose not to breastfeed were being prescribed bromocriptine each year.[2] However, a number of serious adverse events were reported in association with the use of the drug, including seizure, heart attack, stroke, and even death.[3] Starting in 1984, FDA began encouraging Sandoz to include a warning in its labeling and alert doctors to the potential hazards of using the drug for lactation suppression.[4] Not until 1987 did Sandoz implement the requested labeling changes.[5] Still, FDA continued to receive adverse event reports, and recommended that drugs labeled for lactation suppression no longer be used for this indication after a clinical study failed to rule out the risk of stroke.[6] All manufacturers except for Sandoz voluntarily withdrew the indication.[7] FDA initiated withdrawal proceedings in 1994, and in 1995, the FDA withdrew approval for this indication for Parlodel based on the agency's conclusion that the possible risks outweighed the utility of the drug for this use.[8] A wave of lawsuits[9] followed in which plaintiffs' experts claimed that Parlodel causes vasoconstriction, which can result in stroke, seizures, myocardial infarction, and even death. As seen below, claims included strict and negligent products liability (failure to warn, and in some cases, design defect), breach of implied and express warranty, and fraudulent and negligent misrepresentation. News sources report that a number of early cases settled out of court.[10] Nevertheless, many cases were decided in Sandoz's favor on summary judgment motions on the basis that testimony offered by plaintiffs' expert witnesses lacked critical indicia of scientific reliability as set forth in the Supreme Court's *Daubert* to establish causation, in spite of the adverse regulatory action (*e.g.*, *Soldo*, *Hollander*).[11] In addition to the issues of expert testimony and causation, other disputes that arose out of this litigation related to consolidation, statutes of limitations and collateral estoppel based on adverse agency action (*e.g.*, *Yacub*).						

continued

TABLE B-1 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
In re Consolidated Parlodel Litig., 182 F.R.D. 441 (D.N.J. 1998)	Parlodel (on-label prevention of postpartum lactation)	Approved for prevention of lactation in 1980. In Aug. 1994, Sandoz voluntarily withdrew the indication; a few months later, FDA also proposed withdrawing the indication and it was withdrawn in Jan. 1995 (60 FR 3404)	Postpartum lactating women (stroke, seizures, heart attacks)	• Strict products liability (failure to warn) • Negligence • Breach of implied and express warranty • Fraud	**Denying plaintiff's motion for consolidation because individual issues (medical and legal) predominate over the common issues, and thus, consolidation would be unfair to the jury and parties.** The judge agreed that the cases raised common issues related to testing of Parlodel and the manufacturer's correspondence with FDA about the same. Due to the geographic and temporal differences in the manufacturer's marketing program as to each plaintiff, and concerns about prejudice related to admission of evidence of misrepresentation as to one physician (but not all), for example, the judge denied consolidation. The judge also noted that it would be confusing to the jury to apply different state's laws to each case.	N/a

Brasher v. Sandoz Pharma. Corp., 160 F. Supp. 2d 1291 (N.D. Ala. 2001) (medical causation); *see also* Brasher v. Sandoz Pharma. Corp., 2001 WL 36403362 (N.D. Ala. Sept. 21, 2021) (denying summary judgment motion) Globetti v. Sandoz Pharma. Corp., 111 F. Supp. 2d 1174 (N.D. Ala 2000) (holding the same on the issue of medical causation)	Parlodel (on-label prevention of postpartum lactation)	See above	Two postpartum lactating women (stroke)	• Fraud and negligent misrepresentation claims • Failure to warn (negligent and strict liability) • Fraud-on-the-FDA (dismissed under *Buckman*)	**Denying the defendant's motion for summary judgment on medical causation on the grounds that the plaintiffs' expert testimony was sufficiently reliable under *Daubert*.** Sandoz (Novartis) argued that plaintiffs' experts' opinions "are nothing more than unscientific speculation" without "a scientifically appropriate epidemiological study showing an increased risk of stroke associated with Parlodel use."	Uncertain—settlement likely. Both cases dismissed with prejudice on joint stipulation of parties in Feb. 2004. The stipulation and order do not mention a settlement.

continued

TABLE B-1 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					The court held that, although an epidemiological study may be the best evidence, "*Daubert* only requires only that reliable evidence be presented, and that evidence here consists of the animal studies, the medical literature reviews, the ADRs reported to the FDA, and the "general acceptance" of the association between stroke and Parlodel, reflected in several neurology and toxicology textbooks and treatises." From this evidence, causation can be inferred in the absence of other likely causes. The court also noted that reliance on the aforementioned evidence is reasonable given the practical reasons such a study is unavailable.	

Representative cases: • Soldo v. Sandoz Pharmas. Corp., 244 F. Supp. 2d 434 (W.D. Pa. 2003) • Hollander v. Sandoz, 289 F.3d 1193 (10th Cir. 2002), aff'g 95 F. Supp. 2d 1230 (W.D. Okla. 2000) Add'l examples: • Brumbaugh v. Sandoz Pharmas. Corp., 77 F. Supp. 2d 1153 (D. Mont.1999). • Glastetter v. Novartis, 252 F.3d 986 (8th Cir. 2001), aff'g 107 F. Supp. 2d 1015 (E.D. Mo. 2000)	Parlodel (on-label prevention of postpartum lactation)	See above	Postpartum lactating woman (stroke)	• Fraud and negligent misrepresentation claims • Failure to warn • Design defect	**Granting defendant's motion for summary judgment because plaintiffs' expert witnesses could not support medical causation (Daubert hearing).** *Soldo*: excluding testimony that Parlodel can cause ICH because the experts' conclusion "requires too many extrapolations from dissimilar data, too many analytical leaps and involves a loose application of purportedly objective scientific causation standards". Current labeling states that relationship between postmarket adverse reactions (including stroke) and drug not established but warns that drug should not be used for prevention of lactation. Plaintiff also failed to provide admissible evidence on the issues of general and specific causation.	N/a

continued

TABLE B-1 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
• Caraker v. Sandoz Pharmas. Corp., 188 F. Supp. 2d 1026 (S.D. Ill. 2001); *see also* Caraker v. Sandoz Pharmas. Corp., 172 F. Supp. 2d 1018 (S.D. Ill. 2001) • Siharath v. Sandoz Pharmas. Corp., 131 F.Supp.2d 1347 (N.D. Ga. 2001) • Rider v. Sandoz Pharmas. Corp., 295 F.3d 1194 (11th Cir. 2002) • Dunn v. Sandoz Pharmas. Corp., 275 F. Supp. 2d 672 (wM.D.N.C. 2003)					*Hollander:* affirming decision to exclude, among other things, testimony that Parlodel causes vasoconstriction, hypertension, and ensuing stroke on the grounds that, among other problems, studies on animals and on humans with a particular condition could not be reliably extrapolated, and that arguments based on Parlodel's chemical structure and pharmacological properties were too speculative	

Yacub v. Sandoz Pharmaceuticals Corp., 85 F. Supp. 2d 817 (S.D. Ohio 1999) (collateral estoppel), 101 F. Supp. 2d 852 (S.D. Ohio 1998) (statute of limitations)	Parlodel (on-label prevention of postpartum lactation)	See above	Survivorship claim (wife died of thrombosis / heart failure)	• Products liability / state law tort claims (specific claims unclear from cases)	***Collateral Estoppel*: denying the plaintiff's motion for partial summary judgment to preclude Sandoz from litigating the issue of Parlodel's safety as a lactation inhibitor** On the issue of the drug's safety, plaintiff alleged Sandoz was collaterally estopped based on FDA's withdrawal of approval for Parlodel for use as a lactation inhibitor. Court held that FDA's administrative action did not meet the elements of collateral estoppel: no mutuality, issue was not actually litigated, and Sandoz bore the burden of proof (whereas plaintiff does in this action) ***Statute of limitations*: denying the defendant's motion for summary judgment and holding that review of medical report did not trigger statute of limitations**	Undisclosed settlement; the case was dismissed on Aug. 24, 2000.

continued

TABLE B-1 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					Sandoz argued that plaintiff knew or should have known that Parlodel caused the decedent's death because, the decedent reported unusual headaches, the plaintiff consulted with attorneys concerning his wife's death, and reviewed the decedent' medical records, which indicated that Parlodel was one, among other, possible causes of death. Plaintiff later brought suit after reading a newspaper article stating that Sandoz was discontinuing the product and noting pending personal injury litigation. The court rejected Sandoz's argument, holding that the cause of action did not accrue until the plaintiff read the newspaper article; suspecting that Parlodel may have caused the injury did not trigger the statute of limitations.	

Johnson v. Sandoz Pharmas. Corp., 24 Fed. Appx. 533 (6th Cir. 2001), *rev'ing and remanding* 2000 WL 33342287 (W.D. Ky. June 23, 2000)	Parlodel (on-label prevention of postpartum lactation)	See above	Postpartum lactating woman (stroke)	• Products liability / state law (specific claims unclear from cases)	***Statute of limitations:* Reversing and remanding the trial court's grant of defendant's summary judgment motion for a determination on whether the plaintiff acted with reasonable diligence in discovering her injury.** The trial court concluded that the products liability cause of action accrued on the date of the plaintiff's stroke, and was therefore, time barred. The Sixth Circuit held that Kentucky law requires that a plaintiff "be given a reasonable opportunity to discover the causal relationship between the substance and her injury before the statute of limitations clock begins to run against her," and remanded the case for a jury to determine whether the plaintiff exercised reasonable diligence in discovering the injury	Undisclosed settlement; the case was dismissed on Nov. 3, 2003.

continued

TABLE B-1 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Bendet v. Sandoz Pharma. Corp., 208 F.3d 907 (8th Cir. 2002)	Parlodel (on-label prevention of postpartum lactation)	See above	Postpartum lactating woman (stroke)	• Products liability (design defect and failure to warn) • Fraud • Breach of express warranty • Negligent misrepresentation • Negligence per se • Request for punitive damages	**Denying defendant's motion for summary judgment because plaintiff was not judicially estopped as result of decision in another case involving same product.**	Uncertain—settlement possible. Parties stipulated to dismissal but final order dated May 30, 2003, mentions a process failure on the part of plaintiffs.

[1] The following search terms were used: "breastfeeding" or "lactation/ing", "drug," and "malpractice," "clinical trial," "liability," or "consumer protection." Based on these searches, the only litigation identified with respect to lactating persons involved the drug Parlodel.
[2] *See* The Pharma Letter, *Sandoz Faces Parlodel Lawsuits In USA*, Aug. 21, 1994, https://www.thepharmaletter.com/article/sandoz-faces-parlodel-lawsuits-in-usa.
[3] *See human drugs: New drug applications – Sandoz Pharmaceuticals Corp.; approval withdrawn,* 59 FR 44337 (Aug. 23, 1994)
[4] *Id.*
[5] *Id.*
[6] *Id.*
[7] *Id.*
[8] See 60 F.R. 3403 (Jan. 17, 1995). Note that Parlodel is an FDA-approved drug doctors still prescribe today for a variety of uses.
[9] There appears to be approximately 65-70 cases cited on Westlaw. However, there may be more litigation that is not reflected in online databases.
[10] *See* The Pharma Letter, *Sandoz Faces Parlodel Lawsuits In USA*, Aug. 21, 1994, https://www.thepharmaletter.com/article/sandoz-faces-parlodel-lawsuits-in-usa.
[11] Jurisdictional differences with respect to the Parlodel litigation exist. Most notably, Alabama found expert testimony, excluded in other jurisdictions, to pass muster under Daubert, and the case proceeded to trial (*Brasher v. Sandoz Pharmas. Corp.*). Commentators have noted that the Parlodel litigation demonstrates that "[a]pplication of the *Daubert* standard to differential diagnosis testimony has engendered particular disagreement and confusion in the federal courts over the past several years" and observed that "the admissibility of clinical medical evidence has a tremendous impact on the course of product liability litigation and is therefore a determination that should be undertaken carefully." *Just What the Doctor Ordered: The Admissibility of Differential Diagnosis in Pharmaceutical Product Litigation*, 5 VAND. L. REV. 1227, 1229 (2003).

TABLE B-2 Summary of Lawsuits Brought Against Manufacturers for Injuries Suffered from Pregnant Women's On-Label Use of a Drug

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Drugs indicated for pregnancy-related conditions (including oral contraception and fertility treatments)						
Zamfirova v. AMAG Pharmaceuticals, Inc., 2021 WL 2103287 (D.N.J. May 25, 2021) [12]	Makena (prevent preterm birth on-label)	N/A	Mother	• Violation of states' consumer protection laws / fraud	**Granting the defendant's motion to dismiss the class action complaint on preemption grounds** Makena received fast-track approval, but the follow-up FDA mandated post-market trial revealed no statistically significant difference concerning preterm birth (< 35 weeks) between Makena and placebo. AdComm recommended AMAG withdraw Makena. Plaintiffs alleged that AMAG knew from the pre-approval study and incoming data from the post-approval study that Makena was ineffective, and therefore, statements about Makena's efficacy in reducing preterm birth were misleading.	N/a

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					Fraud claims preempted because ad/promo was supported by labeling; interim data from post-market study did not constitute new information that would defeat preemption defense. Indirect purchaser cannot succeed on claim for unjust enrichment; plaintiffs did not purchase Makena directly from AMAG.	
Martin by Martin v. Ortho Pharmaceuticals, 661 N.E.2d 352 (Ill. 1996)	Ortho-Novum (birth control)	Labeling warned against used in pregnant population; regulations also require direct-to-consumer warnings for oral contraceptives	Mother	• Duty to warn (unreasonably dangerous)	**Affirming the grant of summary judgment to the defendant pursuant to the learned intermediary doctrine and declining to create an exception based on FDA regulations regarding oral contraceptives**,[13] for which FDA had promulgated regulations requiring drug manufacturers to issue warnings about oral contraceptives directly to consumers.[14]	N/a

Woodill v. Parke Davis & Co., 402 N.E.2d 194 (Ill. 1980), *aff'g & rem'g* 374 N.E.2d 683 (Ill. App. Div. 5 1978)[15]	Pitocin (induce labor)	N/a	Parents (emotional distress) and child	• Strict liability and negligent product liability • Breach of implied warranty	**Affirming the grant of summary judgment in defendant's favor on the product liability claims. The court agreed that a manufacturer or seller has a duty to warn under strict liability when it knows or should have known of the danger**, but the record did not support such a finding. However, it granted plaintiffs leave to amend the complaint to include knowledge requirement. Pitocin was administered by order of her physician while the fetus was in high station causing serious injury to the child.	N/a
Shepherd v. Vintage Pharmaceuticals, LLC, 310 F.R.D. 691 (N.D. Ga. 2015) *Note*: *not as relevant given the issue and injury*	Eight different oral contraceptives	N/a	100+ women who became unintentionally pregnant (113 accidental pregnancies)	• Strict liability • Negligence • Breach of express and implied warranty • Violation of state consumer protection laws • Unjust enrichment	**Opinion related to class certification, which was denied due to plaintiff-specific nature of each case despite common questions of law/fact.** Manufacturer erred in packaging pills, causing pills to be in the incorrect order and women to become pregnant.[16]	N/a

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Dyson v. Winfield, 113 F. Supp. 2d 35 (D.D.C. 2000), judgment aff'd, 21 Fed. Appx. 2 (D.C. Cir. 2001) *Note: The plaintiff also asserted a medical malpractice claim against the prescribing physician in Dyson v. Winfield, 129 F. Supp. 2d 219 (D.D.C. 2001).*	Provera[17] (induce menstruation)	Contraindicated for known or suspected pregnancy	Child (birth defects and eventual death)	• Failure to warn	**Denying plaintiff's motion to alter or amend the grant of summary judgment in the defendant's favor because the plaintiff failed to show that manufacturer's allegedly inadequate warning was proximate cause of injury.** Specifically, the prescriber stated unequivocally that a different label on the drug would not have affected his decision to prescribe the drug. The court further held that a manufacturer could not be found to have breached its duty of proper preparation, absent any evidence that manufacturer was capable of synthesizing a safer yet similarly effective form of the drug or that manufacturer withheld information from FDA during the labeling process.	N/a

Cerveny v. Aventis, Inc., 783 Fed. Appx. 804 (10th Cir. 2019)[18]	Clomid (fertility treatment, ovulatory dysfunction)	Contraindicated for pregnancy; labeling also contains specific instructions for monitoring patient for signs of pregnancy However, labeling stated: "no causative evidence of a deleterious effect of Clomid therapy on the human fetus has been seen."	Child (physical deformities, e.g., only 3 fingers on one hand)	• Failure to warn (prepregnancy and during pregnancy) • Negligent misrepresentation • Fraud • Breach of implied warranty	**Affirming the district court's grant of summary judgment for the defendant because the plaintiff's claims related to ingestion of Clomid during pregnancy, and the plaintiff ingested Clomid before pregnancy** On the plaintiff's claim for failure to warn of risks of ingesting Clomid before pregnancy, see Cerveny v. Aventis, Inc., 855 F.3d 1091 (10th Cir. 2017) holding that FDA's denial of prior citizen petitions conflict preempted state-law failure-to-warn claims against drug manufacturer.	N/a
Barcal v. EMD Serono, Inc., 2016 WL 1086028 (N.D. Ala. Mar. 21, 2016)	Serophene (fertility treatment) (drug has the same active ingredient as Clomid)	See above	Child (born prematurely with severe cardiac defects)	• Design defect • Failure to warn (strict liability and negligence) • Fraud • State deceptive trade practices act • Punitive damages	**Denying the motion for summary judgment on the failure to warn claim based on her allegation that the warning did not convey the full extent of the risks of cardiac defects, as supported by journal articles indicating an increased risk of occurrence of cardiac defects.**	Uncertain—settlement likely. Case dismissed with prejudice on joint stipulation of parties on Jan. 1, 2019. The stipulation and order do not mention a settlement.

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					But dismissing the design defect claim as duplicative of the failure to warn claim because the adequacy of the warning determines whether the prescription drugs is unreasonably unsafe.	
Barson By and Through Barson v. E.R. Squibb & Sons, Inc., 682 P.2d 832 (Utah 1984)	Delalutin (miscarriage prevention)	1972 package insert indicated that Delalutin was probably effective in pregnant women to prevent habitual and threatened abortion and was safe for that purpose	Child (birth defects)	• Negligence • Breach of warranties of merchantable quality and fitness for use • Strict liability	**Affirming the jury verdict based on substantial evidence that the defendant knew or should have known that progestational agents, including Delalutin, had teratogenic effects, and sufficient evidence that the child's mother would not have been injected with the drug if the defendant had conducted proper testing and/or given a proper warning as to the teratogenic effects of Delalutin.**	Jury award: $1.5 million

Vaccaro v. Squibb Corp., 418 N.E.2d 386 (N.Y. 1980) (bringing claims against manufacturer, physician, and hospital)	Delalutin (miscarriage prevention)	See above	Parents + child (born without arms or legs)	• Negligence • Breach of warranties of merchantable quality and fitness for use • Strict liability • Negligence • Negligent infliction of emotional distress (parents)	**Affirming dismissal of complaint for failure to state an actionable claim as to parents' claim for psychological harm due to injury to their child.** In dismissing the father's claim, the court noted that no duty was owed to him. The mother's claim was dismissed because she failed to demonstrate independent physical injury.[19]	N/a. Information not located on negligence claim

DES CASES

Overview/Summary: Diethylstilbestrol (DES) is a synthetic estrogen that was approved for treatment of miscarriage, preterm labor, and related pregnancy complications. In the 1950s, controlled studies of DES in pregnant women indicated that the drug was likely ineffective.[20] DES was administered to pregnant women for the next 20 years, primarily for prevention of miscarriage. In 1971, a statistical correlation was discovered between DES and clear cell adenocarcinoma of the vagina and cervix in girls and young women who were prenatally exposed to DES. The FDA contraindicated the use of DES in pregnant populations. DES has been linked to a variety of reproductive cancers, fertility problems, and related medical conditions in woman that ingested DES, offspring of mothers that ingested DES in utero ("DES daughters"), and even third-generation populations.[21] DES is still prescribed today (e.g., as estrogen replacement therapy, cancer treatment), but it is no longer indicated for use in pregnant populations.

It is estimated that several million pregnant women ingested DES over a 25-year period, resulting in an estimated 1,000+ individual or class action products liability lawsuits against the pharmaceutical companies that manufactured DES.[22] The majority of the cases were filed in the 1980s/1990s, and the most recent reported case—*Netherland v. Eli Lilly & Co.*, described below—was filed in 2006. Although, some plaintiffs' firms still advertise DES lawsuits on their websites, indicating that cases are likely still being filed today. Many DES cases are not "reported" on legal research websites, but instead settled, went to verdict, or were resolved outside of court, making it difficult to assess the full cost and breadth of DES liability. One 1994 jury verdict is indicative of the financial stakes—the jury awarded $42.3 million to 11 "DES daughters"—awarding $10–12 million to plaintiffs suffering from cancer and up to $2 million to women with reproductive problems.[23]

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
As demonstrated by the below sampling of cases, the "chief barrier to recovery for most DES plaintiffs is identifying the manufacturer who supplied the drug that a particular mother ingested."[24] Several hundred different companies manufactured DES pursuant to the same chemical formula, making it difficult for plaintiffs to identify a liable defendant, but many successful cases relied on theories of joint and several liability or concerted action (*see Bichler* below).						
Netherland v. Eli Lilly & Co., Prod. Liab. Rep. (CCH) P 17547, 2006 WL 626922 (D.D.C. Mar. 13, 2006)	DES	Approved for treatment of miscarriage, preterm labor, and related pregnancy complications in 1947. Contraindicated for use in pregnant women beginning in 1971.	"DES daughter" suffering from malformed uterus and infertility as a result of her in utero exposure to DES. Her mother was prescribed DES for prevention of miscarriage.	• Negligence; strict liability; breach of warranty; negligent misrepresentation; consortium claim; punitive damages	**Granting motion for summary judgment in favor of DES manufacturers where plaintiff failed to produce evidence sufficient to identify Lilly or Premo as the manufacturer of the product that purportedly caused Plaintiff's injuries.**	N/a
Bichler v. Eli Lilly and Co.., 55 N.Y.2d 571, 436 N.E.2d 182 (N.Y. 1982)	DES	Approved for treatment of miscarriage, preterm labor, and related pregnancy complications in 1947.	"DES daughter" that was exposed to DES in utero. Plaintiff suffered from cervical and vaginal cancer at age 17.	• Concerted action.	**Affirming the Appellate Court's judgment in favor of Plaintiff.**	Jury Award: $500,000

		Contraindicated for use in pregnant women beginning in 1971.		• Because all DES was an identical chemical formula and most often was prescribed generically, many plaintiffs could not pinpoint the manufacturer responsible for injury and resorted to "concerted action" liability).	In relevant part, the evidence was sufficient to sustain a verdict against the manufacturer based on a finding that defendant's failure to test DES on pregnant mice before marketing the drug substantially aided/encouraged other manufacturers to do the same (sufficient to establish that defendant acted "in concerted action" with other drug manufacturers). The evidence was sufficient to sustain a finding that cancer to the offspring was a foreseeable risk of ingestion of DES during pregnancy.	
Lyons v. Premo Pharmaceuticals Labs, Inc., 406 A.2d 185 (N.J. 1979)	DES	Approved for treatment of miscarriage, preterm labor, and related pregnancy complications in 1947. Contraindicated for use in pregnant women beginning in 1971.	Suit brought by parents on behalf of "DES daughter" that was prenatally exposed to DES ingested by her mother during pregnancy to prevent abortion. The daughter died from a metastasis of her cervical cancer.	• Joint liability for negligence, breach of warranty, strict liability in tort, false representation	**Affirming that drug companies not within the chain of distribution are not liable for personal injuries suffered by daughter born to mother who ingested DES prenatally.**	N/a

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					The case held that the manufacturer of the bulk DES, and the manufacturer of the pills Plaintiff (mother) ingested are the "proper parties to pay," but that the evidence is insufficient to hold Greeff (the entity that placed the order but never had physical control over DES). Summary judgment was previously granted for all defendants that were not in the chain of distribution. Plaintiffs also settled with two manufacturers in the chain of distribution.	
Drugs indicated for conditions not specific to pregnancy						
Baker v. St. Agnes Hosp. 70 A.D.2d. 400 (N.Y. App. Div. 1979) (bringing suit against Eli Lilly as well)	Dicumarol (anticoagul ant for blood clotting disorders including phlebitis)	Label included contraindication for pregnant and breastfeeding women	Child (brain damage and partial paralysis)	• Products liability (Lilly) • Medical malpractice (hospital)	**Denying Lilly's motion for summary judgment because limiting the warnings related to birth defects to the labeling was insufficient as matter of law.**	Information not located.

	Court held that physician's failure to read the warnings in the labeling did not shield the manufacturer from liability. Manufacturers must keep abreast of knowledge of its products gained through research, adverse reaction reports, scientific literature, etc., and take steps that are reasonably necessary to bring that knowledge to the attention of medical professionals. **NOTE: this case and its holding appear dated and/ or likely impose a higher duty on manufacturers than in other jurisdictions**

Accutane cases: The teratogenic effects of Accutane were well documented when it was approved as an acne treatment. Accutane has had a black-box warning disclosing the high risk of birth defects since 1984. Thus, courts have held that Accutane contained adequate warnings and claims against Roche appear to have been universally dismissed. In addition to the two cases provided as examples below, additional citations can be found at Am. L. Prod. Liab. 3d, Treatise, § 89:110 (May 2023 Updated). We did not identify any major settlements.

The vast majority of Accutane-related litigation involved other side effects of the drug, such as Crohn's disease, irritable bowel syndrome, and depression or suicide, and did not involve pregnant women. In total, over 7,500 lawsuits have been dismissed across the country. See Kristin Compton, Accutane Lawsuits, Drugwatch (Nov. 1, 2022), https://www.drugwatch.com/accutane/lawsuits/.

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TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Clark v. Hoffman-La Roche, Inc., 2006 WL 1374516 (Super. Ct. N.J. May 2, 2006)	Accutane (on-label for acne)	Blackbox warning providing that Accutane is contraindicated for women of childbearing potential unless the patient meets certain requirements Pregnancy Prevention Program, including patient information and informed consent form	Parents; child (unstated birth deformities)	• Defective design under the New Jersey Products Liability Act ("NJPLA") • Failure to warn under the NJPLA; • Breach of implied warranty under the NJPLA; • Punitive damages under the common law and NJPLA; and • Violations of the New Jersey Consumer Fraud Act ("NJCFA").	**Granting defendant's motion to dismiss all claims on basis of adequate warnings**[25] Plaintiff filed complaint seeking to recover for birth defects allegedly caused by ingestion of Accutane Learned intermediary doctrine not an absolute defense because warnings were provided directly to patients. However, warning was adequate as a matter of law. Given adequate warnings, claim of fraud in connection with sale or advertisement of merchandise also failed.	N/a
Banner v. Hoffman-La Roche Inc., 383 N.J. Super 364 (App. Div. 2006)	Accutane (on-label for acne)	See above	Child (unnamed physical and cognitive defects)	• Inadequate warning • Wrongful birth/life[26]	**Granting defendant's motion to dismiss on basis of adequate warnings**	N/a

					Warnings were adequate as a matter of law because the warning provided specific detailed information about the risks of the drug, even though the question of whether the warning is adequate is generally one for the jury to decide.	
In re Depakote, 87 F. Supp. 3d 916 (S.D. Ill. 2015)[27]	Depakote (antiseizure)	Blackbox warning cautioned that the drug "can produce teratogenic effects" such as spina bifida, so use in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus.	**Class action: 617 cases (as of 2017)** Named plaintiff was a child with spina bifida and many other physical and cognitive injuries	• Punitive damages • Strict liability and negligence • Breach of implied and express warranty • Misrepresentation by omission • Fraud and misrepresentation • Intentional infliction of emotional distress (IIED) • Negligent infliction of emotional distress • Willful and wanton conduct	**Denying the defendant's motion for summary judgment on all claims but IIED based on:** • Expert testimony that the label misled readers about the causal relationship between Depakote and birth defects, failed to warn that Depakote was associated with numerous other congenital anomalies, failed to advise on the importance of contraceptive use, and failed to advise that Depakote should only be taken as a last resort.	Over 600 cases were filed against AbbVie by 2018, most of these cases were pending in the Southern District of Illinois. The case was put on hold for parties to focus on settlement negotiations, though it appears no settlement has been reached, and the Illinois MDL has been closed.[28]

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
		Use in Pregnancy Section indicated that antiepilepsy drugs should only be administered to women of childbearing potential if "clearly shown to be essential" to seizure management. PDR reported a 1–2% risk of spina bifida if drug is taken during first trimester (up to 20 times the rate in the general population)			• Genuine issues of fact regarding whether the warning sufficiently apprised the prescribing physicians of Depakote's dangerous propensities, such that these physicians could be considered learned intermediaries. • Evidence that certain representations made in the label, specific affirmations more than just a generalized statement that the product was "safe" or "efficacious," were inaccurate, misleading and sufficient to establish an express warranty, and set forth sufficient evidence of emotional distress resulting from the birth defects to support a negligent infliction of emotional distress claim.	

					• Evidence to support the claim that the defendant acted wantonly in failing to update the label information and failing to warn of certain risks all while aggressively marketing Depakote; a reasonable jury could conclude that the plaintiff was entitled to punitive damages.	
Willis v. Abbott Laboratories, 2017 WL 5988215 (W.D. Ky. 2017)	Depakote (antiseizure, bipolar disorder / mental illness)	See above	Child (spina bifida and many other physical and cognitive injuries)	• Failure to warn • Design defect • Negligent misrepresentation	**Granting defendant's motion to dismiss plaintiff's failure-to-warn claim on preemption grounds** because there was clear evidence the FDA would not have approved a change to the Depakote label adding a developmental delay warning prior to the plaintiff's injuries (and design defect as duplicative); and	See above

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					Denying defendant's motion to dismiss negligent misrepresentation claim, based on several statements made on the Depakote label concerning the uncertainty of the risk of birth defects because there was evidence that plaintiff's doctor relied on these statements during the pregnancy with the child.	
Barron v. Abbott Laboratories, 529 S.W.3d 795 (Mo. 2017)	Depakote (antiseizure)	See above	Child (spina bifida and many other physical and cognitive injuries)	• Strict liability products liability • Negligence • Breach of implied and express warranty • Misrepresentation by omission • Fraud and misrepresentation • Intentional infliction of emotional distress (IIED)	**Affirming the jury award when considering the evidence in plaintiff's favor**, which included evidence that Abbott was aware from studies that Depakote was more dangerous than its label suggested and that it failed to conduct independent research to evaluate the risk, despite this knowledge.	Jury award: $38 million ($15 million in compensatory damages; $23 in punitive damages)

				• Negligent infliction of emotional distress • Punitive damages		
In re Zoloft (Sertraline hydrochloride) Prod. Liab. Litig., 176 F. Supp. 3d 483 (E.D. Pa. 2016), aff'd sub nom. 858 F.3d 787 (3d Cir. 2017)[29]	Zoloft (on-label antidepressant)	Limited warnings about potential for increased risk of neonatal complications, including persistent pulmonary hypertension of the newborn and instructed patient to "notify their physician if they become pregnant or intend to become pregnant during therapy."	**MDL: approximately 300 cases** Child (cardiac birth defects)	• Products liability (defective design) • Misrepresentation	**Granting motion for summary judgment because plaintiffs' expert witnesses could not support general causation (Daubert case).** The court held that for an expert to opine on general causation in a toxic tort action, the expert must account for and analyze the full universe of epidemiological studies and explain why that research does not contradict or undermine the expert's opinion.	N/a

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Fields v. Eli Lilly & Co., 116 F. Supp. 3d 1295 (M.D. Ala 2015)	Prozac (antidepressant)	Pregnancy Category C; label instructs patients to tell their doctor if they are pregnant, breastfeeding, or plan to become pregnant	Other + child (congenital heart defect)	• Failure to warn	**Denying defendant's motion for summary judgment because there were genuine issues of material fact as to whether doctor would have prescribed antidepressant had manufacturer provided a stronger warning about the risks of birth defects and whether plaintiff ingested Prozac during her pregnancy.**	Uncertain—settlement likely. Case dismissed by joint stipulation on Mar. 23, 2015. The motion does not mention a settlement.
Horne v. Novartis Pharmaceuticals Corp., 541 F. Supp. 2d 768 (W.D.N.C. 2008)	Lotensin HCT (on-label hypertension)	Package insert contained warning and information about use in pregnancy regarding cardiovascular risks and death when used during second and third trimesters; directed patients to discontinue drug if they became pregnant	Child (died at 19 days of heart and kidney defects)	• Breach of implied warranty of merchantability • Negligence in design, manufacture, R&D, testing, processing, distribution and sale of drug • Wantonness • Failure to warn • Fraud, misrepresentation, and suppression	**Granting defendant's motion to dismiss claims of wantonness, fraud, and failure to warn on preemption grounds; denying motion on negligence and breach of warranty of merchantability** Plaintiff discontinued treatment during first trimester. Alleged that Novartis should have known of the prenatal risk during the first trimester and included a warning on the drug's label	Uncertain—settlement likely. Parties filed a joint stipulation of dismissal on Feb. 11, 2009. The motion does not mention a settlement.

					Held: claims requiring a label change preempted; negligence claims plead sufficiently	
McCuin v Watson Pharmaceuticals, Inc., 2008 WL 11444178 (E.D. Tex. Feb. 11, 2008); *see also* 2009 WL 10707939 (E.D. Tex. Aug. 17, 2009); (granting manufacturer's motion to for summary judgment / motion to dismiss for failure to prosecute claim)	Enalapril (ACE inhibitor for high blood pressure)	No warnings related to ingestion during first trimester	Parent + child (ventricular septal defect and patent ductus arteriosus, congestive heart failure, and atrial septal defect and right ventricular hypertrophy)	• Negligence • Strict liability defective design • Strict liability failure to warn • Breach of implied warranty • Fraud • Negligent misrepresentation • Gross negligence	**Denying manufacturer's motion to dismiss.** With respect to the fraud/ misrepresentation claim, the Court observed that "it would be reasonable to find that Defendants had intended reliance of the alleged misrepresentations even before conception because of the presumed safety during this interim period until the discovery of conception."	N/a
Anderson v. Janssen Pharmaceuticals, Inc., No. 2330 EDA 2014, 2016 WL 2909234 (Pa. Super. Ct. May 11, 2016)	Topamax[30] (migraines on-label)	Drug labeled as a Category C drug (i.e., birth defects detected in animals but no conclusive evidence in humans)	Parents + child (severe bilateral cleft lip and palate, connected to hearing loss and speech problems)	• Negligent failure to warn	**Affirming $3 million jury award for non economic damages and medical expenses**	Jury award: $3 million

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					Drug labeled as a Category C, not D (known risk). When Anderson became pregnant, her doctors instructed her to discontinue other category D medications but not Topamax as a category C. Prescribers indicated that had the drug been labeled as a Category D or had the warnings disclosed the risk of cleft palate, they likely would have altered their prescribing decisions. Court held that preemption does not apply because there were ways that Janssen could have strengthened its warnings before the label is actually changed; also rejected learned intermediary defense because evidence at trial demonstrated Jannsen knew of a causal relationship between drug and specific birth defects, including cleft palate, but failed to disseminate the information to physicians	

United States ex rel. Jackson v. Ventavia Research Group, LLC, No. 1:21-CV- 00008, 2023 WL 2744394, (E.D. Tex. Mar. 31, 2023)	COVID-19 vaccine	Clinical trials, on-label use	Relator employee (no injury to pregnant women or children alleged)	• False Claims Act	**Granting defendants' motion to dismiss** Qui tam suit alleging violation of False Claims Act based on clinical trial protocol violations and other ethical/safety concerns related to clinical trials due to mismanagement by research group tasked with managing clinical trials for Pfizer's COVID-19 vaccine. One such violation was administering the vaccine or placebo to pregnant women, despite their exclusion in the protocol, and failing to report this participating to Pfizer	N/a
Kiker v. SmithKline Beecham Corp., 2026 WL 8189286 (S.D. Ohio Dec. 15, 2016)	Paxil (depression on-label use)	1992 label instructed pregnant women to consult with their doctor before taking	Mother + child (infant respiratory distress syndrome and ventricular septal defect [serious heart defect])	• Negligent pharmacovigilance (under Ohio Products Liab. Act) • Fraud	**Denying defendant's motion to dismiss on preemption grounds**	Undisclosed settlement. Case dismissed by joint motion of the parties on Aug. 1, 2017.

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
		1995 label changed pregnancy risk category from B to C but retained language that preclinical animal studies revealed no evidence of teratogenic effects Sept 2005 label later revised to warn of "the increased risk for cardiovascular malformations" for prenatal exposure Dec 2005 changed from Category C to D and added new data to Warnings section under Teratogenic Effects		• Breach of express warranty • Negligence • Strict liability	Plaintiff alleged manufacturer received hundreds of adverse event reports related to Paxil exposure during pregnancy and refused to conduct animal testing or inform the medical community of this significant finding, as well as knew of potential teratogenic effects and nevertheless indicated in the label that the cause of death of rat pups was unknown despite evidence to the contrary. Held: on issues of fraud and breach of express warranty, court found that allegations that label did not adequately inform physician of prescribing risk was sufficient to survive motion to dismiss; preemption defense rejected because facts do not show that FDA would have refused a stronger warning label—no efforts from GSK; stronger warnings were added in consult with FDA.	

Hayes v. SmithKline Beecham Corp., 2009 WL 4912178 (N.D. Okla. Dec. 14, 2009)	Paxil (depression on-label use)	See above	Mother + child (heart defect)	• Products liability • Negligence • Punitive damages	**Denying defendant's motion to dismiss on preemption grounds** Plaintiff used Paxil during her first trimester, which caused her child's heart defect; alleged that GSK knew or should have known of potential teratogenic effects at the time Same preemption holding. No clear evidence that FDA would have refused a stronger warning label. Facts at least raise triable issues of fact as to punitive damages (e.g., avoiding studies requested by foreign regulator for concern of results)	Undisclosed settlement. Case dismissed by joint motion of the parties on Jan. 26, 2010.
			Over-the-counter drug			
In re Acetaminophen – ASD-ADHD Prod. Liab. Litig., 2022 WL 17348351 (S.D.N.Y Nov. 14, 2022); 2023 WL 3045802 (S.D.N.Y. Apr. 21, 2023); 2023 WL 3126636 (S.D.N.Y Apr. 27, 2023)	OTC acetaminophen (on-label use)	"If pregnant or breastfeeding, ask a health professional before use."	MDL (ASD, ASD-ADHD)	• Failure to warn • Strict liability for design defect • Negligence • Negligent and strict liability misrepresentation • Breach of implied warranty	Plaintiffs alleged that had they known acetaminophen could cause ASD-ADHD when taken while pregnant, they would not have done so.	Ongoing

continued

TABLE B-2 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
				• Violation of states' consumer protection laws (2023 WL 3126636)	2022 WL 17348351 (**failure to warn**): FDA OTC regulations require warning that all drugs intended for systemic absorption contain a pregnancy and breastfeeding warning instructing patients to consult with their doctors before using the product. Court rejected preemption argument on the basis that regulations permitted Walmart (OTC manufacturer) to include more specific warnings in addition to the required warnings 2023 WL 3045802 (**consumer protection and products liability**): FDCA 379r expressly preempts state law claims not related to products liability. Court dismissed consumer protection claim on basis that such economic claims are not analogous to products liability and therefore preempted, but denied motion to dismiss remaining claims.	

	2023 WL 3126636 (**misrepresentation**): ad with a pregnant woman and statement regarding the incredibly safe safety profile of the drug did not constitute affirmative misrepresentation (claim dismissed); alleged failure to include safety information sufficient to survive motion to dismiss for negligent misrepresentation on an omission theory

[12] Other class actions lawsuits involving allegations that AMAG misrepresented the effectiveness of Makena were transferred to New Jersey. *See, e.g.*, Barnes v. AMAG Pharmaceuticals, Inc. 2020 WL 759121 (W.D. Mo. Feb. 14, 2020).

[13] The majority of jurisdictions do not recognize an exception to the learned intermediary doctrine for manufacturers of contraceptive. However, a minority of jurisdictions do recognize such exception. *See Martin*, 661 N.E.2d at 356 (collecting cases).

[14] 21 C.F.R. § 310.501.

[15] A number of settlements and jury verdicts have favored plaintiffs based on allegations of improper use of Pitocin (e.g., excessive doses). See Miller & Zois, Maryland Malpractice: Pitocin Settlements and Verdicts, https://www.millerandzois.com/medical-malpractice/birth-injuries/pitocin-birth-injury/pitocin-birth-settlement-maryland/ for examples.

[16] It is unclear whether any settlements were reached. However, the manufacturer claimed that it had only been able to confirm the sale of one defective pack to a patient. More than 100 women say birth control mix-up led to unplanned pregnancies, CBS News (Nov. 12, 2015), https://www.cbsnews.com/news/women-sue-drug-company-claiming-defective-birth-controls-led-to-unplanned-pregnancies/.

[17] Other cases involving Provera/Depo-Provera include *Ambrosini v. Labarraque*, 966 F.2d 1464 (D.C. Cir. 1992) (bringing actions against manufacturer and prescribing physician).

See also Am. L. Prod. Liab. 3d, Product Citator § 127 (May 2023 Update) (collecting cases)

continued

TABLE B-2 Continued

[18] *Sullivan v. Aventis, Inc.*, 2015 WL 4879112 (S.D.N.Y. Aug. 13, 2015) (granting and denying motion to dismiss in part); *Morgan v. Christman*, 1990 WL 137405 (D. Kan. July 20, 1990) (denying defendant physician's motion for summary judgment) (also listed in Table 4); *Lust By and Through Lust v. Merrell Dow Pharmaceuticals, Inc.*, 89 F.3d 594 (9th Cir. 1994) (holding that the district court was justified in concluding that plaintiff's causation expert's testimony did not meet the Daubert standard for admissibility).

[19] New York has since reversed course, at least in the case of a medical malpractice claim, allowing a mother to recover for damages under a theory of negligent infliction of emotion distress. *See generally* Alicia A. Ellis, *Better Late Than Never: New York Finally Closes the "Gap" in Recovery Permitted for Negligent Infliction of Emotional Distress in Prenatal Medical Malpractice Cases*, 80 St. John's L. Rev. 725 (2006).

[20] National Academies of Sciences, Engineering, & Medicine, Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies, vol. 1, 238 (Anna Mastroianni et al. ed) (1994).

[21] Two "DES granddaughters" claimed that their premature births and related disabilities were caused by damage to their mothers' reproductive organs from DES exposure *in utero. See, e.g., Lyons v. Premo Pharmaceuticals Labs, Inc.*, 406 A.2d 185 (N.J. 1979); *see also Enright v. Eli Lilly & Co.*, 570 N.E.2d 198 (N.Y. 1991) (dismissing plaintiff's personal injury claims—fraud, breach of warranty, strict liability, and negligence—against the DES manufacturer because extending liability to a third generation would unreasonably stretch traditional tort concepts beyond manageable bounds and potentially inhibit the creation or availability of important prescription drugs); *Sorrells v. Eli Lilly and Company*, 737 F. Supp. 678 (D.D.C. 1990) (granting defendant's motion to dismiss plaintiff's strict liability and negligence claims because the "law of Maryland at this time does not extend defendant's duty to the unborn granddaughter of a mother who ingested DES.").

[22] National Academies of Sciences, Engineering, & Medicine, WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES, vol. 1, 238 (Anna Mastroianni et al. ed) (1994).

[23] *Jury Awards $42.3 Million To Women in Drug Lawsuit*, The Associated Press (Jan. 9, 1994), https://www.nytimes.com/1994/01/09/nyregion/jury-awards-42.3-million-to-women-in- drug-lawsuit.html.

[24] *See e.g., Gianvito v. Premo Pharma. Labs., Inc.*, 19 N.Y.3d 812 (N.Y. 2012), *aff'g* 93 A.D.3d 546 (N.Y. App. Div. 1 2012) (declining to adopt "market share" theory of liability under New Jersey law where plaintiffs failed to identify the manufacturer of DES they consumer).

[25] *Hunt by Hunt v. Hoffman-La Roche, Inc.*, 785 F. Supp. 547 (D. Md. 1992) (granting defendant's motion for summary judgment under learned intermediary doctrine, concluding that manufacturer warned prescribing doctor of risks associated with Accutane). The plaintiff also filed suit against the prescribing doctor. *Id.* at 549 & n.3.

[26] There is jurisdictional variation on whether a wrongful birth suit is recognized.

[27] Earlier cases that went to trial resulted in mixed jury verdicts. *See* Michelle Llamas, *Depakote Lawsuits*, Drugwatch (Nov. 4, 2022), https://www.drugwatch.com/depakote/lawsuits/; *see e.g., Barron v. Abbott Laboratories*, 529 S.W.3d 795 (Mo. 2017) (discussed below)

[28] *See* Am. L. Prod. Liab. 3d, Treatise, § 89.81 (May 2023 Update) for other cases involving injuries due to in utero exposure to Depatoke; *see, e.g.*, *Hutchens v. Abbott Laboratories, Inc.*, 2017 WL 5622688 (N.D. Ohio 2017) (denying plaintiff's motion for a new trial after the jury unanimously found in the defendant's favor); *Rheinfrank v. Abbott Laboratories, Inc.*, 199 F. Supp. 3d 749 (S.D. Ohio 2015) (granting defendant's motion to dismiss plaintiff's failure-to-warn claim on preemption grounds); *Muhammad v. Abbott Labs., Inc.*, 203 N.E.3d 1001 (Ill. App. Ct., 1st Dist., 4th Div. 2022) (reversing grant of summary judgment on grounds of judicial estoppel because physician's negligence does not automatically relieve a drug manufacturer of liability for failure to warn).

[29] Other cases involving Zoloft include: *J.C. by and through Michelle C. v. Pfizer, Inc.* 814 S.E.2d 234 (W.V. 2018) (holding that expert testimony was required to support claim that label for drug failed to adequately warn of risks of use during pregnancy and affirming the grant of summary judgment to Pfizer); *Bealer v. Hoffman-LaRoche, Inc.*, 729 F. Supp. 43

[30] *See also Gurley v. Janssen Pharmaceuticals, Inc.*, 113 A.3d 238 (Pa. Super. Ct. 2015) (affirming $11 million jury verdict, awarded based on the finding that manufacturer failed to adequately warn of the risk of birth defects; the appellate court agreed that the claim was not preempted because the defendant could have unilaterally changed its label warnings per FDA's Changes Being Effected regulations); *Czimmer v. Janssen Pharmaceuticals, Inc.*, 122 A.3d 1043 (Pa. Super. Ct. 2015) (affirming $4.2 million jury verdict).

TABLE B-3 Summary of Lawsuits Against Manufacturers for Injuries Suffered from Pregnant Women's Off-Label Use of Drugs

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
			Off-label use in pregnant women			
In re Zofran (Ondansetron) Products Liab. Litig., 541 F. Supp. 3d 164 (D. Mass. 2021), *aff'd by In re* Zofran (Ondansetron) Products Liab. Litig., 57 F.4th 327 (1st Cir. 2023)	Zofran (antiemetic off-label for pregnancy-related nausea / morning sickness)	Not contraindicated for pregnancy and labeling does not contain an enhanced form of warning for use in pregnant women (as of 2021)	Mothers + children (primarily orofacial defects and cardiac ventricular and/or septal defects) Cases consolidated into MDL	• **Failure to warn** • Negligence • Fraudulent misrepresentation • Violation of state consumer protection laws • Wrongful death • Loss of consortium	**Defendant's motion for summary judgment granted on preemption grounds[31] (defeating 425 lawsuits)** Plaintiffs alleged manufacturer's off-label marketing caused physicians to prescribe Zofran off-label, in turn, causing birth defects, and that labeling failed to adequately warn physicians of the risks of such off-label use. Defendant-manufacturer's BOP met based on evidence requested labeling changes on multiple occasions and FDA, fully informed of justifications for warning, denied such changes. Thus, requiring the changes would misbrand the drug.	Pending

In re Zofran (Ondansetron) Products Liab. Litig., 261 F. Supp. 3d 62 (D. Mass 2017)	Zofran (see above)	See above	See above	• See above	**Denying certification of plaintiff's request on state law** Plaintiffs aver that GSK knew of risk of birth defects from preclinical and from adverse event reports and medical literature. Based on these assertions, plaintiffs claim that GSK failed to perform an adequate study of the safety of ingesting Zofran during pregnancy and promoted Zofran for use in pregnancy despite knowing its teratogenic risks; further, plaintiffs allege liability extends to patients who ingested the generic because it is reasonably foreseeable that such promotion would result in patients being prescribed the generic	N/a

continued

TABLE B-3 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Brown v. GlaxoSmithKline, LLC, 523 P.3d 132 (Oregon Ct. App. 2022) (suit against both manufacturer and hospital)	Zofran (see above)	See above	Mother and child (cardiac defects)	• Strict product liability	**Denying defendant hospital's motion for summary judgment because a genuine issue of material fact existed as to whether the hospital was a seller engaged in the business of selling the drug and thus falling within the scope of a seller of a product strictly liable for injuries caused by that product.** Hospital prescribed Zofran to treat 7-week-pregnant plaintiff's morning sickness. The court rejected the defendant's contention that a seller must advertise, promote, or package the product and be a wholesale or retail dealer.	Appeal pending: review accepted by Oregon Supreme Ct. on June 1, 2023

In re Zofran (Ondansetron) Products Liab. Litig., 2018 WL 2291316 (D. Mass May 18, 2018)	See above	See above	See above	• See above	**Denying plaintiff's motion to amend** New claim asserting that off-label promotion constituted fraudulent misrepresentation could have been discovered earlier and therefore motion was untimely	N/a
T.H. v. Novartis Pharmaceuticals Corp., 407 P.3d 18 (Cal. 2017)[32]	Terbutaline (asthma medicine used off-label to prevent preterm birth)	Off-label use	Twin children (severe neurological injuries, including autism, inability to speak, abnormal motor functions)	• Failure to warn • Negligent and intentional misrepresentation (based on alleged representations that drug was safe for off-label use) • Negligence • Concealment	**Affirming decision of appellate court to remand the case to the trial court to grant plaintiffs leave to amend the causes of action for negligence and negligent misrepresentation.** Twins injured by generic product, prescribed off-label, 6 years after Novartis transferred the rights to the product. Plaintiff alleged that Novartis knew or should have known that terbutaline carried a substantial prenatal risk based on studies conduct predivesture and failed to update its label warning	Case appears to have been closed based on information for Case No. D067839 in the 4th Appellate District Division 1 of Cal.

continued

TABLE B-3 Continued

Case	Drug	Labeling Information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					Held: brand-name manufacturers have a duty to use ordinary care in warning about the safety of their drugs, regardless of whether the injured party was dispensed the brand-name or generic version of the drug (in reliance on the brand-name manufacturer's warning); liability continues after rights to the product are transferred	

Whitener v. PLIVA, 606 Fed. Appx. 762 (5th Cir. 2015)	Metoclopramide (generic of Reglan) (off-label for morning sickness)	Not contraindicated for pregnancy	Mother, husband, son (born prematurely with birth defects)	• Failure to warn of danger during pregnancy • Off-label promotion for a dangerous use	**Affirming summary judgment in defendant's favor because plaintiffs failed to establish that birth defects were caused by off-label promotion.** Specifically, the prescriber stated that his "clinical . . . judgment" and "experience"—and not any promotional activities on the part of the defendants—that led him to prescribe metoclopramide to Mrs. Whitener. The court declined to rule on whether the brand-name manufacturer could be liable harm caused by the generic for off-label promotion or whether the off-label promotion claim was essentially a preempted failure to warn claim. Trial court also dismissed failure to warn claims against a generic manufacture as preempted under *Mensing v. PLIVA* in an earlier case	N/a

[31] *See also* Nate Raymond, *GSK Defeats 425 Lawsuits Alleging Zofran Causes Birth Defects*, Reuters (June 1, 2021), https://www.reuters.com/legal/litigation/gsk-defeats-425-lawsuits-alleging-zofran-causes-birth-defects-2021-06-01/.

[32] The risk of liability on this expansive theory of duty is likely unique to California. *See Anand Agneshwar & Jocelyn Wiesner, T.H. v. Novartis Pharmaceuticals Corp., Top Food and Drug Cases*, 2017 & Cases to Watch, 2018, Food & Drug L. Inst., https://www.fdli.org/2018/07/t-h-v-novartis-pharmaceuticals-corp/. Other jurisdictions have generally declined to hold brand-name manufacturers liable for injury caused by products other than their own.

TABLE B-4 Summary of Lawsuits Against Practitioners for Injuries Suffered from Pregnant Women's Use of Drugs

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Terrebonne v. Floyd, 767 So.2d 758 (La. App. 1 Cir. 2000)	Depo-Provera (on-label endometrio sis); also Xanax (anxiety)	Depo-Provera PI warnings states that "the first injection be given only during the first 5 days after the onset of a normal menstrual period" to avoid inadvertently administering the drug to a pregnant woman Xanax labeling also indicated that drug "can potentially cause fetal harm" and that the "possibility that a woman of child bearing potential may be pregnant at the time of institution of therapy should be considered"	Mother + child (breached duty of care to mother and child) (child born with skull malformation and stunted skull growth requiring multiple surgeries)	• Medical malpractice	**Reversing the trial court's grant of summary judgment because a genuine issue of material fact existed as to whether gynecologist violated standard of care by relying on results of pregnancy test before administering drug.** Doctor prescribed Depo-Provera to woman 18 days outside of window recommended in labeling, and with knowledge that a pregnancy test would be unlikely to be positive this early in pregnancy (first trimester). Trial court dismissed based on plaintiff's failure to offer expert testimony on the standard of care required of an OBGYN.	Outcome on remand not identified.

					Held: expert testimony not needed as whether doctor violated the standard of care by relying on the results of a test he admittedly knew may have been false and then administering drug contrary to the plain language in the manufacturer's label are issues within the purview of the lay jury; deviation from manufacturer's specific warning was sufficient evidence to make a prima facie showing of negligence
Dyson v. Winfield, 113 F. Supp. 2d 44 (D.D.C. 2000); *see also* 129 F. Supp. 2d 22 (D.D.C. 2001) (granting plaintiff's motion for reconsideration of the dismissal of the plaintiff's request for extraordinary child rearing expenses); 113 F. Supp. 2d 35 (granting summary judgment motion as to the manufacturer)	Provera (on-label use for menstruation problems)	Contraindicated for pregnant women Patient information section directs physicians to advise patients that drug exposure in the first trimester can cause birth defects	Mother and child (severe hearing, sight, ingestion, and intellectual disability, and eventually death at age 3)	• State wrongful death statute • State wrongful survival statute • Negligent breach of duty to inform	Denying defendant's motion to exclude expert testimony and summary judgment motion based on the expert testimony was reliable and relevant and a material issue of fact existed as to whether the physician breached the standard of care by prenatally exposing plaintiff to Provera and failing to inform mother of risks of prenatal exposure.

continued

TABLE B-4 Continued

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
					Patient sued physician, alleging that he negligently prescribed drug to her while she was pregnant, causing her child to be born with birth defects and eventually die.	
Morlino v. Medical Ctr. of Ocean County, 706 A.2d 721 (N.J. 1998), aff'g Morlino v. Medical Ctr. of Ocean County, 684 A.2d 944 (N.J. Sup. Ct., App. Div. 1996)	Cipro (Ciprofloxacin)	Physician Desk Reference (PDR) states that the drug "should not be used in children or pregnant women" Category C drug (potential risk to fetus)	Mother	• Medical malpractice	**Affirming the jury decision in favor of the defendants on the basis that the failure to admit the PDR was a harmless error**[33] Eight and one-half month pregnant patient brought suit after having been prescribed an antibiotic for a sore throat, the day after which her fetus was dead. The plaintiff alleged that she was not warned that the drug might pose a risk to the fetus, and the doctor claimed that he prescribed the drug based on his professional opinion that the risks outweighed the benefits.	N/a

					NOTE: The trial court refused to admit the PDR warning. **The Appellate Court held that the PDR when accompanied by expert testimony was admissible to establish the standard of care, but that a departure from the PDR is not prima facie negligence**	
McClendon v. Williams, 110 So.3d 216 (La. Ct. App., 2d. Cir. 2013), *rev'd by* McClendon v. Williams, 126 So.3d 1270 (La. 2013)	Versed (anesthesia); Decadron (anti-inflammatory)	Versed: Category D drug (demonstrated risk to fetus) Decadron: Category C drug (potential risk to fetus)	Mother (miscarriage, and emotional distress)	• Medical malpractice	**The La. Supreme Court reversed the appellate court's grant of summary judgment based on lack of medical causation.** Plaintiff, who suffered a miscarriage, alleged that defendants breached the standard of care in failing to properly interpret the laboratory diagnostics indicating a positive pregnancy test, in referring a pregnant patient to radiology, and in administering medications contraindicated for pregnant patients.	Outcome on remand not identified.

continued

TABLE B-4 Continued

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Richardson v. Miller, 44 S.W.3d 1 (Tenn. Ct. App. 2000)	Infusion pump and terbutaline (off-label as a tocolytic agent (i.e., prevent preterm birth)	Label includes warning regarding the use of terbutaline for tocolysis due to adverse events reported when drug is administered intravenously	Mother (heart attack)	• Medical malpractice	**Vacating the jury verdict in defendant's favor and ordering a new trial because the trial court improperly excluded evidence relating to off-label use of drug in question more probably than not affected outcome of trial, requiring vacation of verdict and new trial.** Among other things, the court held that the prescription drug's labeling or its reference in Physician's Desk Reference, when introduced along with other expert evidence on standard of care, is admissible in medical malpractice action to assist in determining whether drug presented unacceptable risk to patient;	Outcome on retrial not identified.

Moore ex rel. Moore v. Memorial Hosp. of Gulfport, 825 So.2d 658 (Miss. 2002)	Diovan (hypertension on-label use)	Blackbox warning regarding potential injury and death to fetus due to prenatal exposure	Mother + child (end-stage kidney failure, hypertension, developmental delays, hyperactive gag reflex)	• Medical malpractice, including failure to monitor baby after delivery (hospital) • Negligent in selling drug contraindicated for pregnant women (pharmacy)[34]	**Granting the pharmacy's motion for summary judgment on the basis of the learned intermediary doctrine, and denying the hospital's motion for summary judgment** Learned intermediary doctrine extends to pharmacies, and pharmacist was under no duty to advise plaintiff of possible side effects or second guess the appropriateness of a valid prescription, unless the pharmacist knew about a contraindication or knew that prescriptions were inconsistent with recommended dosage guidelines	Outcome as to claim against the hospital not identified.

continued

TABLE B-4 Continued

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Serigne v. Ivker, 808 So.2d 783 (La. App. Ct., 4th Cir., 2002)	Phenobarbital (antiseizure)	Not approved by the FDA until 2022	Parents + child (cerebral palsy, seizures, congenital microcephaly, developmental delays)	• Medical malpractice	**Granting summary judgment on the basis that the parents failed to prove by a preponderance of the evidence that drug prescribed during pregnancy caused child's cerebral palsy.**[35] Although an expert testified that the physician violated the standard of care by prescribing phenobarbital to a pregnant person, no expert testimony establishing that the drug caused the birth defects was obtained	N/a
Hogle v. Hall By and Through Evans, 916 P.2d 814 (Nev. 1996)	Accutane (acne)	Blackbox warning providing that Accutane is contraindicated for women of childbearing potential unless the patient meets certain requirements, including a negative serum pregnancy test and receive written warnings	Child by father and later grandmother (severe cognitive defects)	• Medical malpractice	**Affirming the court's award of additur without a new trial** where the physician had prescribed Accutane after the mother provided incorrect information regarding her menstrual cycle and after he failed to follow the guidelines appearing in the Physician's Desk Reference regarding the prescription of Accutane, a birth-defect causing drug.	Jury award: $2.93 million (including $300,000 in additur)

Winje by Winje v. Upjohn Co. 156 A.D.2d 987 (N.Y. Sup. Ct., App. Div 1989)	Provera (also Delalutin (miscarriage prevention))	1972 package insert indicated that Delalutin was probably effective in pregnant women to prevent habitual and threatened abortion and was safe for that purpose	Child by mother (physical deformities)	• Medical malpractice	**Reversing and granting summary judgment in defendant-doctor's favor, holding that physician was not liable to parents of child born with birth defects absent evidence indicating that physician departed from acceptable standard of care in medical community in his treatment of mother.** In short, the plaintiff alleged that the physician breached his duty of care by failing to inform her of the risk of Provera, which had been prescribed to her before she came under defendant's care.	N/a

continued

TABLE B-4 Continued

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Harbeson v. Parke-Davis, Inc, 656 P.2d 483 (Wash. 1983), aff'd 746 F.2d 517 (9th Cir. 1984)	Dilantin (antiseizure)	Unclear from case and not available on Drugs@FDA	Parents + child (severe physical and cognitive developmental disabilities)	• Medical malpractice—wrongful birth[36] • Wrongful life • Lack of informed consent	**Affirming that Washington recognizes a claim for wrongful life under which plaintiff-child can recover and wrongful birth under which plaintiff-parents can recover. The court also affirmed the trial court's finding that the defendants breached their standard of care by failing to conduct a literature search or to consult other sources**, in regard to the effects of Dilantin during pregnancy, even though the plaintiffs Leonard and Jean Harbeson specifically asked all three Madigan physicians of possible birth defects associated with the mother's consumption of Dilantin during pregnancy.	Unidentified amount of damages awarded in bench trial.

Lynch v. Bay Ridge Obstetrical & Gynecological Assoc., 532 N.E.2d 1239 (N.Y. Ct. App. 1988)	Provera (menstruation inducing)	Contraindicated for pregnant women; PDR includes recommendation to advise pregnant women of risk of congenital abnormalities	Mother (aborted fetus)	• Medical malpractice	**Reversing dismissal of complaint and holding that the plaintiff's decision to abort was not a superseding cause to the defendant's negligence as a matter of law,** thus allowing a claim against a physician for negligently failing to diagnose plaintiff's pregnancy and then prescribing a drug whose use was contraindicated in such patients	Uncertain outcome.
Canesi ex cel. Canesi v. Wilson, 730 A.2d 805 (N.J. 1999)	Provera (menstruation inducing)	Contraindicated for pregnant women; PDR includes recommendation to advise pregnant women of risk of congenital abnormalities	Child and mother (bilateral limb abnormalities)	• Informed consent • Wrongful life	**Affirming that PDR, which contained warnings of the general and specific risks that progestational agent posed to fetus was not, of itself, sufficient evidence to establish a standard of care for purposes of wrongful birth action.**	N/a

continued

TABLE B-4 Continued

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Spano v. Bertocci, 299 A.D.2d 335 (N.Y. App. Div. 2d Dep't 2002)	Depakote (antiseizure)	Blackbox warning cautioned that the drug "can produce teratogenic effects" such as spina bifida, so use in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. Use in Pregnancy Section indicated that antiepilepsy drugs should only be administered to women of childbearing potential if "clearly shown to be essential" to seizure management.	Mother + Child (spina bifida)	• Medical malpractice • Lack of informed consent	**Reversing jury verdict in favor of mother and child based on lack of informed consent. The court held that the claim when asserted prenatally was essentially a wrongful life action, which is not recognized in New York. The court also held that the doctor's failure to inform the mother plaintiff of the risks was not the proximate cause of the infant's injury because she had been warned of the risks by other physicians.**	Outcome following order for retrial uncertain.

		PDR reported a 1–2% risk of spina bifida if drug is taken during first trimester (up to 20 times the rate in the general population)			Doctor allegedly breached standard of care by failing to remove mother from drug and by failing to warn mother of inherent risk of birth defects. The jury found in favor of the defendant on the medical malpractice claim and in favor of the plaintiffs on the informed consent claim. After this case, retrial was ordered due to jury misconduct. *See* Spano v. Bertocci, 22 A.D.3d 828 (N.Y. App. Div. 2d Dep't 2005)	
R.R. By and through Stowell v. Dandade, 2017 WL 2117386 (N.M. Ct. App. Apr. 25, 2017)	Zoloft (antidepressant)	Limited warnings about potential for increased risk of neonatal complications, including persistent pulmonary hypertension of the newborn and instructed patient to "notify their physician if they become pregnant or intend to become pregnant during therapy."	Child (neurodegenerative disorder)	• Medical malpractice	**Affirming the trial court's exclusion of expert testimony and summary judgment on the basis that the plaintiff's expert's opinion was untested and unsupported as to the neurodegenerative disorder suffered by the plaintiff's child allegedly as the result of plaintiff's prenatal ingestion of Zoloft.** Note that the expert was a Ph.D. in pharmacology, not a medical doctor, and therefore his testimony was based on the biological mechanism that could have caused the disease.	N/a

continued

TABLE B-4 Continued

Case	Drug	Labeling information	Plaintiff / Injury	Claims	Case Description	Settlement Amount / Jury Verdict (If Applicable)
Davis v. United States, 2015 WL 11142426 (N.D. Ga. Mar. 31, 2015)	Methotrexate (arthritis)	Pregnancy Category C; label instructs patients to tell their doctor if they are pregnant, breastfeeding, or plan to become pregnant	Child	• Medical malpractice	**Granting the defendant's summary judgment motion on the basis that the scientific literature did not support the expert's "damaged sperm" theory, where drug was prescribed to father, or show the plaintiffs' child's birth defects were of a type associated with methotrexate use by mother or father.**	N/a
Littlefield v. Rand, 961 N.E.2d 162 (Mass. App. Ct 2012)	Depo-Provera (birth control)	Depo-Provera PI warnings states that "the first injection be given only during the first 5 days after the onset of a normal menstrual period" to avoid inadvertently administering the drug to a pregnant woman	Mother and child (unspecified birth defects)	• Wrongful birth	**Affirming that the jury verdict in favor of the defendant was not against the weight of the evidence based on claims regarding the admissibility of evidence**	N/a

			After the plaintiff's contraception (Depo-Provera) failed and her child was born with disabilities, the plaintiff brought a wrongful birth suit brought against the physician who failed to diagnose the plaintiff's pregnancy alleging that she would have aborted the fetus

[33] The court noted that the plaintiff's credibility was seriously undermined at trial.

[34] *See also Nichols v. Central Merchandise, Inc.*, 817 P.2d 1131 (Kan. Ct. App. 1991) (granting summary judgment in favor of defendant pharmacy on the basis that under learned intermediary doctrine, the pharmacy and its pharmacist owed no duty to warn customer of potential side effects of drug prescribed by customer's treating physician).

[35] Note that claims against the manufacturer were dismissed because it met its duty to warn the prescribing physician.

[36] Note on wrongful life claims: courts differ on whether to recognize such claims. *Cf. Bruggeman v Schimke (1986) 239 Kan 245, 718 P2d 635* (rejecting all damages for "wrongful life.").

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Commissioned Paper: State Statutes Regarding Fetal Research, Fetal Personhood, Fetal Homicide and Child Abuse/Neglect & Substance Abuse

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INTRODUCTION

This paper provides an overview of statutes from the fifty states and the District of Columbia (D.C.) that may be relevant to the conduct of biomedical research with pregnant women, in effect as of January 1, 2024. Specifically, it covers statutes that implicate research involving a fetus (excluding statutes solely applicable to embryonic stem cell research), statutes focused on child endangerment that might be applicable to a fetus, and those implicating fetal personhood and fetal homicide. The table does not show state statutes that do not fit neatly into these categories but may have implications for research involving pregnant and lactating women. The table also does not include any relevant federal statutes. The table cites judicial decisions and attorney general's (AG) opinions in which the listed statutes are interpreted. The sheer breadth of the topics is not conducive to comprehensiveness, and we may not have identified all relevant statutes, cases, and AG opinions. The research methodology supporting the attached table is described in detail below.

This paper is intended for informational purposes only and does not constitute legal advice. The authors make no warranty or guarantee regarding the accuracy, completeness or suitability of the information contained herein. This paper does not create an attorney-client relationship between the authors and any reader. Readers should consult a qualified legal professional before taking any action based on the information in this paper.

RESEARCH METHODS

To conduct our review, we consulted legal research databases (Westlaw and Lexis), secondary sources (e.g., peer-reviewed literature, law review articles), and internet sources (i.e., news articles, reports, state legislation trackers, and state surveys) to identify relevant state statutes and case law interpreting those statutes. We prepared a table that consolidated and synthesized the information we discovered on this topic. The table is organized by state and divided into subtopics: (1) Fetal Research; (2) Fetal Personhood; (3) Fetal Homicide; and (4) Child Abuse/Neglect & Substance Abuse. The table summarizes enacted state statutes and related case law and AG opinions as of January 2024, excluding any currently proposed legislation.

(1) *Fetal Research*

To address the possible effect of state laws on clinical studies involving pregnant women, we searched the legal databases for state statutes that explicitly prohibit or limit research on pregnant women and/or fetuses/embryos. Our search was limited to state statutes that use the terms "fetus" (and its variations, e.g. "fetal), "embryo" (and its variations, e.g. "embryonic"), and "pregnant" (and its variations, e.g. "pregnancy") in conjunction with the term "research." Where applicable, we identified relevant exceptions to these statutes, including for medical treatment, and the requirements for maternal consent.[1]

(2) *Fetal Personhood*

Fetal personhood laws encompass state statutes that grant explicit legal rights to fetuses. Many of these laws define "human being" or "person" (either throughout a state's legal code or specifically in its criminal statutes) to include fetuses or the "unborn." In conducting our search, we used a broad definition of "fetal personhood" to include statutes that describe embryos and/or fetuses as persons or unborn children. Due to the fast-moving political environment surrounding the adoption of state fetal personhood laws, we primarily consulted secondary sources, including news reports and online legislation trackers in addition to searching within the legal databases. To validate our findings, we conducted searches within the legal databases and identified relevant statutes using the terms "unborn child" and "fetus" (and its variations, e.g. "fetal").

[1] We did not find any references to paternal consent in any of the statutes pertaining to research with a fetus.

In states without an explicit fetal personhood law, we searched for related case law to assess whether "person" or "human being" in the state's criminal code has been determined to include fetuses or the unborn. We also searched the legal databases for relevant attorney general opinions.

(3) *Fetal Homicide*

Fetal homicide laws include general state homicide statutes that are applicable to fetuses, as well as laws criminalizing feticide as a separate crime. To identify fetal homicide laws, we relied on a report, *State Laws on Fetal Homicide and Penalty-enhancement for Crimes Against Pregnant Women*, published by the National Conference of State Legislatures[2]. Relying primarily on the NCSL report's research methodology, we conducted an additional search of the legal research databases, using terms such as "fetal," "homicide" and "feticide" (with variations) to identify fetal homicide laws enacted after the publication of the report.

(4) *Child Abuse/Neglect & Substance Abuse*

This category encompasses two distinct types of conduct. "Child abuse" and "child neglect" laws penalize acts or omissions that harm a child's health or welfare. If state law classifies fetuses as children, child abuse could be found in research that involves a pregnant participant ingesting or otherwise using an experimental substance that is determined to have caused physical injury to a fetus, and child neglect could be alleged by characterizing the research as a denial of appropriate care or an exposure to harmful conditions. The "substance abuse" provisions in the table involve criminalizing the use (abuse) of an illegal substance (occasionally alcohol use as well) by a pregnant woman; in some states, such an act is prosecuted as child abuse/neglect. To identify statutes on child abuse/neglect and substance abuse, we searched the legal research databases for "child abuse," "child welfare," or "child neglect." We did not necessarily distinguish between civil and criminal actions. For each relevant statute, we searched the legal research databases for case law and attorney general opinions involving pregnant individuals, along with whether a "fetus" or an "unborn" person is included in the definition of the term "child."

[2] National Conference of State Legislatures. *Research and Policy: State Laws on Fetal Homicide and Penalty-enhancement for Crimes Against Pregnant Women* (NCSL, May 1, 2018). https://www.ncsl.org/research/health/fetal-homicide-state-laws.aspx. [https://perma.cc/6YSM-22NX] (accessed February 20, 2024).

TABLE C-1 State Statutes and Relevant Case Law and AG Opinions as of January 1, 2024

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Alabama	Ala. Code § 26-23F-5(c) "No person shall use an unborn infant, living or deceased, in research or experimentation." Ala. Code § 26-23F-3(12) An "unborn infant" is "a human being in utero at any stage of development regardless of viability." Additionally, "no person shall knowingly accept compensation or payment for the sale, transfer, distribution, acceptance, use, or attempted use of the fetal organs, tissue, or bodily remains of a deceased unborn infant for research, therapy, transplantation, or experimentation."	Ala. Code § 26-23H-3(7) An "unborn child" is "a human being, specifically including an unborn child in utero at any stage of development, regardless of viability." Ala. Const. Art. I, § 36.06 "[I]t is the public policy of this state to recognize and support the sanctity of unborn life and the rights of unborn children, including the right to life."	Ala. Code § 13A-6-1 The homicide statute defines "person" to "include an unborn child in utero at any stage of development, regardless of viability."	Ala. Code § 26-15-3.2 – 3.3 It is a felony to expose a child to "a controlled substance, chemical substance, or drug paraphernalia . . . It is an affirmative defense . . . that the controlled substance was provided by lawful prescription for the child, and that it was administered to the child in accordance with the prescription instructions provided with the controlled substance." The law is not violated "if the responsible person was the mother of the unborn child, and she was, or there is a good faith belief that she was, taking that medication pursuant to a lawful prescription" or, in the case of a "non-prescription FDA approved medication or substance . . . as directed or recommended by a physician or a health care provider."

	"No institution, entity, or individual shall knowingly provide any compensation or payment to any other person, organization, or entity for the removal, transfer, storage, processing, preservation, quality control, implantation, transportation, distribution, disposal, or other manner of disposition of the bodily remains of a deceased unborn infant for research, therapy, transplantation, experimentation, or any other prohibited purpose under this chapter."			*Hicks v. State*, 153 So. 3d 53 (Ala. 2014) (holding that ingestion of cocaine while pregnant constitutes child endangerment under Ala. Code § 26-15-3.2). *Ex parte Ankrom*, 152 So. 3d 397 (Ala. 2013) (holding that the term "child" includes an "unborn child").
Alaska	None found	Alaska Stat. Ann. § 11.81.900 (66) An "unborn child" is "a member of the species Homo sapiens, at any stage of development, who is carried in the womb."	Alaska Stat. Ann. § 11.41.150 ; Alaska Stat. Ann. § 11.41.160 ; Alaska Stat. Ann. § 11.41.170 "[M]urder of an unborn child," "manslaughter of an unborn child," and "criminally negligent homicide of an unborn child" are felonies.	Alaska Stat. Ann. § 47.17.290 "Child abuse or neglect means the physical injury or neglect, mental injury, sexual abuse, sexual exploitation, or maltreatment of a child under the age of 18 by a person under circumstances that indicate that the child's health or welfare is harmed or threatened thereby."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Arizona	None found	ARIZ. REV. STAT. ANN. § 1-219 "[A]n unborn child at every stage of development [is granted] all rights, privileges and immunities available to other persons." *Isaacson v. Brnovich*, 610 F. Supp. 3d 1243 (D. Ariz. 2022) (temporarily enjoining Arizona from enforcing ARIZ. REV. STAT. ANN. § 1-219, as applied to abortion care that is otherwise permissible under state law, until ongoing litigation is resolved). ARIZ. STAT. ANN. § 36-2151 Arizona defines an "unborn child" as "the offspring of human beings from conception until birth," and defines "conception" as "the fusion of a human spermatozoon with a human ovum."	ARIZ. REV. STAT. ANN. § 13-1105 "A person commits first-degree murder if intending or knowing that the person's conduct will cause death, the person causes the death of another person, including an unborn child, with premeditation . . . [t]his section applies to an unborn child in the womb at any stage of its development." Exceptions include cases where the person is performing a lawful abortion with consent, providing medical treatment to the pregnant woman or unborn child, or is the unborn child's mother.	ARIZ. REV. STAT. ANN. § 13-3623 "Under circumstances likely to produce death or serious physical injury, any person who causes a child . . . to suffer physical injury . . . is guilty of . . . a felony. . ." "Child" is defined as an individual under the age of 18. *Reinesto v. Superior Ct. of State In & For Cnty. of Navajo*, 182 Ariz. 190, 894 P.2d 733 (Ct. App. 1995) (holding that Arizona may not prosecute a woman for child abuse based on prenatal conduct, such as use of heroin, that causes injury to her child post-birth).

Arkansas	ARK. CODE ANN. § 20-17-802 "A person shall not perform any biomedical or behavioral research on: (1) A fetus born alive as the result of a legal abortion unless the research is for the exclusive benefit of the fetus so born; or (2) A fetus born dead as the result of a legal abortion or on any fetal tissue produced by the abortion." "A person shall not buy, sell, give, exchange, or barter or offer to buy, sell, give, exchange, or barter any fetus born dead as a result of a legal abortion or any organ, member, or tissue of fetal material resulting from a legal abortion."	ARK. CONST. Amend. LXVIII, § 2 "The policy of Arkansas is to protect the life of every unborn child from conception until birth, to the extent permitted by the Federal Constitution."	ARK. CODE ANN. § 5-1-102 (13)(B)(i-iii) "i. (a) As used in §§5-10-101 – 5-10-105 and 5-4-604, "person" also includes an unborn child in utero at any stage of development. (b) "Unborn child" means offspring of human beings from conception until birth. ii. This subdivision (13)(B) does not apply to: (a) An act that causes the death of an unborn child in utero if the act was committed during a legal abortion to which the woman consented, including an abortion performed to remove an ectopic pregnancy or other nonviable pregnancy when the embryo is not going to develop further". . . (b) An act that is committed pursuant to a usual and customary standard of medical practice during diagnostic testing or therapeutic treatment; (c) An act that is committed in the course of medical research, experimental medicine, or an act deemed necessary to save the life or preserve the health of the woman . . . [a]ssisted reproduction technology activity, procedure, or treatment . . . or [a]n act occurring before transfer to the uterus of the woman of an embryo created through in vitro fertilization."	ARK. CODE ANN. § 12-18-103 14(B)(i)(a)-(b) "Child or juvenile means an individual who is from birth to eighteen (18) years of age." Child neglect includes: "(a) Causing a child to be born with an illegal substance present in the child's bodily fluids or bodily substances as a result of the pregnant mother's knowingly using an illegal substance before the birth of the child; or (b) At the time of the birth of a child, the presence of an illegal substance in the mother's bodily fluids or bodily substances as a result of the pregnant mother's knowingly using an illegal substance before the birth of the child." "Illegal substance means a drug that is prohibited to be used or possessed without a prescription."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	"A person shall not possess either a fetus born dead as a result of a legal abortion or any organ, member, or tissue of fetal material resulting from a legal abortion. This provision does not apply to: (1) Physicians conducting a legal abortion or pathologist examining the outcome of a legal abortion; (2) Employees, agents, or servants of a physician performing a legal abortion or pathologist involved in a pathological examination post a legal abortion; (3) Staff, faculty, students, or governing body of higher or secondary education institutions within the scope of relevant courses and research; (4) Licensed physicians, employees, agents, and servants engaged in medical research; (5) Licensed physicians conducting standard autopsy examinations."		"." (iii) Nothing in this subdivision (13)(B) shall be construed to allow the charging or conviction of a woman with any criminal offense in the death of her own unborn child in utero." Ark. Code Ann. § 5-10-101 to 5-10-105 Causing "the death of a person" is capital murder, murder in the first degree, murder in the second degree, manslaughter, or negligent homicide.	

California	Cal. Health & Safety Code § 123440 "It is unlawful for any person to use any aborted product of human conception, other than fetal remains, for any type of scientific or laboratory research or for any other kind of experimentation or study, except to protect or preserve the life and health of the fetus. "Fetal remains," as used in this section, means a lifeless product of conception regardless of the duration of pregnancy. A fetus shall not be deemed to be lifeless for the purposes of this section, unless there is an absence of a discernible heartbeat."	None found	Cal. Penal Code § 187(a) "Murder is the unlawful killing of a human being, or a fetus, with malice aforethought." The statute "shall not apply to any person who commits an act that results in the death of a fetus if . . . (1) The act complied with the former Therapeutic Abortion Act . . . or the Reproductive Privacy Act, (2) The act was committed by a holder of a physician's and surgeon's certificate . . . in a case where, to a medical certainty, the result of childbirth would be death of the person pregnant with the fetus or where the pregnant person's death from childbirth, although not medically certain, would be substantially certain or more likely than not, [or] (3) It was an act or omission by the person pregnant with the fetus or was solicited, aided, abetted, or consented to by the person pregnant with the fetus."	Cal. Penal Code § 273a It is a crime for "[a]ny person who, under circumstances or conditions likely to produce great bodily harm or death, willfully causes or permits any child to suffer, or inflicts thereon unjustifiable physical pain or mental suffering, or having the care or custody of any child, willfully causes or permits the person or health of that child to be injured, or willfully causes or permits that child to be placed in a situation where his or her person or health is endangered." *Reyes v. Superior Ct.*, 75 Cal. App. 3d 214, (Cal Ct. App. 1977) (holding that the term "child" as used in the statute does not include "an unborn child or fetus").

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Colorado	Colo. Rev. Stat. Ann. § 25-2-111.5 "No physician or institution that performs procedures for the induced termination of pregnancy shall transfer such tissue for valuable consideration to any organization or person that conducts research using fetal tissue or that transplants fetal tissue for therapeutic purposes."	None found	None found	Colo. Rev. Stat. Ann. § 18-6-401 "A person commits child abuse if such person causes an injury to a child's life or health, or permits a child to be unreasonably placed in a situation that poses a threat of injury to the child's life or health, or engages in a continued pattern of conduct that results in malnourishment, lack of proper medical care, cruel punishment, mistreatment, or an accumulation of injuries that ultimately results in the death of a child or serious bodily injury to a child. . . . Child means a person under the age of sixteen years." *People v. Jones*, 464 P.3d 735 (Colo. 2020) (holding that a "person," as the term is used in the state's child abuse statute, does not include a fetus who suffers injuries in utero but is later born alive).

Connecticut	None found	None found	None found	Conn. Gen. Stat. Ann. § 46b-120 (1), (4) & (5) "Child means any person under eighteen years of age who has not been legally emancipated. . ." "A child may be found neglected who . . . (A) has been abandoned, (B) is being denied proper care . . ., or (C) is being permitted to live under conditions . . . injurious to the well-being of the child." "A child may be found abused who . . . has been inflicted with physical injury. . ." Conn. Gen. Stat. Ann. § 45a-717(g)(2)(b) A "court may [terminate] parental rights . . . if it finds . . . the child has been denied, by reason of an act or acts of parental commission or omission . . . the care . . . necessary for the child's physical . . . well-being." *In re Valerie D.*, 613 A.2d 748 (Conn. 1992) (holding that § 45a-717 does not permit termination of parental rights based on mother's prenatal conduct, in this case, injecting heroin hours before labor).

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
District of Columbia	D.C. CODE ANN. § 7-2086.01 "The District shall not . . . penalize a person for . . . any act or omission by an individual during the individual's pregnancy based on the potential or actual impact on the individual's health or pregnancy. . ."	None found	None found	D.C. CODE ANN. § 4-1341.01 "(1) "Child" means a person under 18 years of age. (2) "Child abuse" means harm or threatened harm to a child's health or welfare by a person responsible for the child's health or welfare, which occurs through the intentional infliction of physical or emotional injury. . . (3) "Child neglect" means harm to a child's health or welfare which occurs through the failure to provide adequate food, clothing, shelter, education, or medical care."
Delaware	None found	None found	None found	DEL. CODE ANN. tit. 11, § 1100. "(1) "Abuse" means causing any physical injury to a child through unjustified force. . . torture, negligent treatment, sexual abuse, exploitation, maltreatment, mistreatment or any means other than accident." (2) "Child" shall mean means any individual less than 18 years of age."

Florida	FLA. STAT. ANN. § 390.0111 (6)	None found	FLA. STAT. ANN. § 775.021 (5)	FLA. STAT. ANN. § 827.03
	"No person shall use any live fetus or live, premature infant for any type of scientific, research, laboratory, or other kind of experimentation either prior to or subsequent to any termination of pregnancy procedure except as necessary to protect or preserve the life and health of such fetus or premature infant."		"Whoever commits . . . a criminal offense . . . and thereby causes the death of, or bodily injury to, an unborn child commits a separate offense if the provision or statute does not otherwise specifically provide a separate offense for such death or injury to an unborn child. . . . The punishment . . . is the same as the punishment provided . . . had the injury or death occurred to the mother of the unborn child. . . . This subsection does not permit the prosecution: 1. Of any person for conduct relating to an abortion for which the consent of the pregnant woman . . . has been obtained . . .; 2. Of a person for providing medical treatment of the pregnant woman or her unborn child; or 3. Of a woman with respect to her unborn child." "'[U]nborn child" means a member of the species *Homo sapiens*, at any stage of development, who is carried in the womb."	'"Child abuse" means: 1. Intentional infliction of physical or mental injury upon a child; 2. An intentional act that could reasonably be expected to result in physical or mental injury to a child; or 3. Active encouragement of any person to commit [such] an act."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Georgia	None found	GA. CODE ANN. § 1-2-1(b), (e) (as amended by § 3 of the Living Infants Fairness and Equality ("LIFE") Act, H.B. 481 (Ga. 2019)). "Natural person" means any human being including an unborn child. . . . "Detectable human heartbeat" means embryonic or fetal cardiac activity or the steady and repetitive rhythmic contraction of the heart within the gestational sac. . . . "Unborn child" means a member of the species Homo sapiens at any stage of development who is carried in the womb." *SisterSong Women of Color Reprod. Just. Collective v. Kemp,* 472 F. Supp. 3d 1297 (N.D. Ga. 2020) declared the LIFE Act unconstitutional and permanently enjoined its enforcement on the	GA. CODE ANN. § 16-5-80. "[T]he term "unborn child" means a member of the species homo sapiens at any stage of development who is carried in the womb. . .. A person commits the offense of feticide if he or she willfully and without legal justification causes the death of an unborn child by any injury to the mother of such child, which would be murder if it resulted in the death of such mother, or if he or she, when in the commission of a felony, causes the death of an unborn child." "Voluntary manslaughter of an unborn child" occurs if a "person causes the death of an unborn child under circumstances which would otherwise be feticide and if such person acts solely as the result of a sudden, violent, and irresistible passion resulting from serious provocation sufficient to excite such passion in a reasonable person; provided, however, that, if	GA. CODE ANN. § 16-5-70 A person commits the offense of cruelty to children when such person "(a) . . . willfully deprives the child of necessary sustenance to the extent that the child's health or well-being is jeopardized . . . (b) . . . . maliciously causes a child under the age of 18 cruel or excessive physical or mental pain. (c) . . . with criminal negligence causes a child under the age of 18 cruel or excessive physical or mental pain." GA. CODE ANN. § 51-1-46(d)(1) & (2)(B) "A person injured by an individual drug abuser may bring an action . . . for damages against a person who participated in illegal marketing of the controlled substance used by the individual abuser. . . . If a

ground that the U.S. Supreme Court in *Roe v. Wade* had concluded that "person" includes only postnatal children.

That judgment was reversed on appeal in *SisterSong Women of Color Reprod. Just. Collective v. Kemp*, 40 F.4th 1320 (11th Cir. 2022), on the ground that the U.S. Supreme Court had subsequently decided *Dobbs v. Jackson Women's Health Organization* 597 U.S. 215 (2022), overturning *Roe v. Wade*.

there should have been an interval between the provocation and the killing sufficient for the voice of reason and humanity to be heard, of which the jury in all cases shall be the judge, the killing shall be attributed to deliberate revenge and be punished as feticide."

Prosecution in not permitted under §16-5-80 "for any medical treatment of the pregnant woman or her unborn child," of "any woman with respect to her unborn child," or "for conduct relating to an abortion for which the consent of the pregnant woman, or person authorized by law to act on her behalf, has been obtained" or "is implied by law."

plaintiff . . . proves that the defendant participated in illegal marketing of a market area controlled substance actually used by the individual abuser who injured the plaintiff, the defendant is presumed to have injured the plaintiff and to have acted willfully and wantonly if the plaintiff is one of the following: (A) A parent, legal guardian, child, spouse, or sibling of the individual abuser;
(B) A child whose mother was an individual abuser while the child was in utero."

A "market area controlled substance" is defined as "a specified controlled substance or marijuana."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Hawaii	None found	None found	None found	Haw. Rev. Stat. Ann. § 587A-4 "'"Child" means a person who is born alive and is less than eighteen years of age." The law applies against persons who inflict "damage or injury to a child's physical or psychological health or welfare" including providing the child "with dangerous, harmful, or detrimental drugs . . . except when a child's family administers drugs to the child as directed or prescribed by a practitioner."
Idaho	Idaho Code Ann. § 39-9303 (10) Idaho Code Ann. § 18-604 (5) "Unborn infant" has the same meaning as "fetus" and "unborn child," which each mean "an individual organism of the species Homo sapiens from fertilization until live birth."	Idaho Code Ann. § 32-102 "A child conceived, but not yet born, is to be deemed an existing person so far as may be necessary for its interests, in the event of its subsequent birth."	Idaho Code Ann. § 18-4001 "Murder is the unlawful killing of a human being including, but not limited to, a human embryo or fetus . . . which results in the death of a human being."	Idaho Code Ann. § 18-1501 "Any person who . . . willfully causes or permits any child to suffer, or inflicts thereon unjustifiable physical pain or mental suffering, or having the care or custody of any child, willfully causes or permits the person or health

IDAHO CODE ANN.
§ 39-9306

Under Idaho's Unborn Infants Dignity Act, "
(1) . . . no person shall knowingly sell, transfer, distribute, donate, accept, use or attempt to use the body or bodily remains of an aborted infant. . . .
(2) . . . no person shall knowingly aid or abet any such sale, transfer, distribution, other unlawful disposition, acceptance, use or attempted use of the body or bodily remains of an aborted infant. . . .
(3) . . . no person or public institution operating in Idaho shall knowingly use an unborn infant or the bodily remains . . . . of an aborted infant . . . in animal or human research, experimentation or study, or for transplantation, except: (a) For diagnostic or remedial procedures that have the purpose of promoting the life or health

IDAHO CODE ANN.
§ 39-9302 (1)(a)

"Deceased unborn infants deserve the same respect and dignity as other deceased human beings."

IDAHO CODE ANN.
§ 18-8801 ; § 18-604; § 18-502

"Fetus" and "unborn child" each mean "an individual organism of the species Homo sapiens from fertilization until live birth."

of such child to be injured, or willfully causes or permits such child to be placed in such situation that its person or health is endangered" commits a crime punishable by imprisonment.

IDAHO CODE ANN.
§ 16-1602

Under Idaho's Child Protective Act, "'' abused" means any case in which a child has been the victim of conduct or omission resulting in skin bruising, bleeding, malnutrition, burns, fracture of any bone, head injury, soft tissue swelling, failure to thrive or death, and such condition or death is not justifiably explained, or where the history given concerning such condition or death is at variance with the degree or type of such condition or death, or the circumstances indicate that such condition or death may not be the product of an accidental occurrence."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	of the unborn infant or the unborn infant's mother . . . (4) . . . no person shall knowingly experiment upon an unborn infant who is intended to be aborted unless the experimentation is therapeutic to the unborn infant."			"Child" means an individual who is under 18. A 1991 opinion by the Idaho Attorney General contends that the state has "a compelling interest in protecting potential human life from gestational drug abuse and in further protecting a child's right to be born with a sound mind and body. In the instance of known gestational drug abuse the state's compelling interest will override the woman's interest in personal privacy, bodily integrity and parental autonomy and permit some degree of state intervention." 1991 Idaho Op. Atty. Gen. 5, Op. Atty. Gen., 91-1 (Feb. 1, 1991), 1991 WL 495720.

Illinois	410 Ill. Comp. Stat. Ann. 110/45 "A person may not knowingly, for valuable consideration, purchase or sell embryonic or cadaveric fetal tissue for research purposes. . . . [T]he giving or receiving of reasonable payment for the removal, processing, disposal, preservation, quality control, storage, transplantation, or implantation of the tissue does not constitute purchase or sale. This Section does not prohibit reimbursement for removal, storage, or transportation of embryonic or cadaveric fetal tissue for research purposes."	None found	720 Ill. Comp. Stat. Ann. §§5/9-1.2, 5/9-2.1, 5/9-3.2. An "unborn child" is "any individual of the human species from the implantation of an embryo until birth," and causing the death of an unborn child at any stage of pre-natal development can qualify as intentional homicide, voluntary manslaughter, involuntary manslaughter, or reckless homicide. Intentional homicide, voluntary manslaughter, involuntary manslaughter, and reckless homicide do not apply when a pregnant woman consents to an abortion that results in the death of her unborn child, nor does they apply to acts that "were committed pursuant to customary standards of medical practice during diagnostic testing or therapeutic treatment."	325 Ill. Comp. Stat. Ann. 5/3 ""Child" means any person under the age of 18 years." Child abuse involves creating "a substantial risk of physical injury to such child by other than accidental means which would be likely to cause death, disfigurement, impairment of physical or emotional health, or loss or impairment of any bodily function; committing or allowing to be committed any sex offense; torture, excessive corporal punishment, female genital mutilation against the child; giving child access to controlled substances."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Indiana	IND. CODE ANN. § 35-46-5-1.5 "'[F]etal tissue" includes tissue, organs, or any other part of an aborted fetus. . . . A person who intentionally acquires, receives, sells, or transfers fetal tissue commits unlawful transfer of fetal tissue, a Level 5 felony."	IND. CODE ANN. § 16-34-2-3 "Any fetus born alive shall be treated as a person under the law, and a birth certificate shall be issued certifying the child's birth even though the child may subsequently die, in which event a death certificate shall be issued. Failure to take all reasonable steps, in keeping with good medical practice, to preserve the life and health of the live born person shall subject the responsible persons to Indiana laws governing homicide, manslaughter, and civil liability for wrongful death and medical malpractice."	IND. CODE ANN. § 35-42-1-1, IND. CODE ANN. § 35-42-1-3, IND. CODE ANN. 35-42-1-4 A person who "kills a fetus in any stage of development" commits murder, voluntary manslaughter, or involuntary manslaughter. These sections do not apply to lawful abortions. IND. CODE ANN. § 35-42-1-6 "A person who knowingly or intentionally terminates a human pregnancy with an intention other than to produce a live birth or to remove a dead fetus commits feticide, a Level 3 felony." "This section does not apply to (1) the pregnant mother whose pregnancy is terminated; (2) a person who in good faith provides medical treatment to a pregnant woman that results in the accidental or unintentional termination of the pregnancy; or (3) a physician licensed under IC 25-22.5 who, upon the request of a pregnant woman, performs a medical procedure to terminate her pregnancy, even if the procedure is not authorized under IC 16-34-2-1."	IND. CODE ANN. § 34-23-2-1 The definition of "child" "includes a fetus that has attained viability." An action for "wrongful death" can be brought against the person whose wrongful act or omission caused the injury or death of a child." The law excludes lawful abortions.

Iowa	Iowa Code Ann. § 146D.1	Iowa Code Ann. § 146B.1	Iowa Code Ann. §707.7	Iowa Code Ann. § 232.68
	"A person shall not knowingly acquire, provide, receive, otherwise transfer, or use a fetal body part in this state, regardless of whether the acquisition, provision, receipt, transfer, or use is for valuable consideration." This section does not apply to "diagnostic or remedial tests, procedures, or observations which have the sole purpose of determining the life or health of the fetus in order to provide that information to the pregnant woman or to preserve the life or health of the fetus or pregnant woman; . . . the pathological study of body tissue, including genetic testing, for diagnostic or forensic purposes; [or] a fetal body part if the fetal body part results from a spontaneous termination of pregnancy or stillbirth and is willingly donated for the purpose of medical research."	"Unborn child" is defined as an "individual organism of the species homo sapiens from fertilization until live birth."	"Any person who intentionally terminates a human pregnancy, with the knowledge and voluntary consent of the pregnant person, after the end of the second trimester . . . where death of the fetus results commits feticide. Any person who intentionally terminates a human pregnancy, with the knowledge and voluntary consent of the pregnant person, after the end of the second trimester . . . where death of the fetus does not result commits attempted feticide. . . . This section shall not apply to a physician licensed in this state to practice medicine or surgery . . . when in the best clinical judgment of the physician the termination is performed to preserve the life or health of the pregnant person or of the fetus and every reasonable medical effort not inconsistent with preserving the life of the pregnant person is made to preserve the life of a viable fetus."	"Child" is defined as any person under 18. Child abuse means "any non-accidental physical injury or . . . mental injury to child's intellectual or psychological capacity as evidenced by an observable and substantial impairment in the child's ability to function within the child's normal range . . . commission of a sexual offense . . . failure . . . to provide for the adequate food, shelter, clothing, medical or mental health treatment . . . necessary for the child's health and welfare. . . . An illegal drug is present in a child's body as a direct and foreseeable consequence of the acts or omissions of the person responsible for the care of the child."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	The term "fetal body part" means a cell, tissue, organ, or other part of a fetus that is terminated by an abortion." "Fetal body part" does not include: "(1) Cultured cells or cell lines derived from a spontaneous termination of pregnancy or stillbirth and willingly donated for the purposes of medical research. (2) A cell, tissue, organ, or other part of a fetus that is terminated by an abortion that occurred prior to July 1, 2018. (3) All cells and tissues external to the fetal body proper."			

Kansas	KAN. STAT. ANN. § 65-67a01 (d) "'Fetal tissue" means any tissue, cells or organs obtained from a dead human embryo or fetus after an abortion or after a stillbirth." KAN. STAT. ANN. § 65-67a02 "Nothing in this act shall be construed as either permitting or prohibiting the use of fetal tissue for any type of scientific, research, laboratory or other kind of experimentation either prior to or subsequent to any abortion or stillbirth."	KAN. STAT. ANN. § 65-6732 "(1) The life of each human being begins at fertilization; (2) unborn children have interests in life, health and well-being that should be protected . . . the laws of this state shall be interpreted and construed to acknowledge on behalf of the unborn child at every stage of development, all the rights, privileges and immunities available to other persons, citizens and residents of this state, subject only to the constitution of the United States, and decisional interpretations thereof by the United States supreme court and specific provisions to the contrary in the Kansas constitution and the Kansas Statutes Annotated."	KAN. STAT. ANN. § 21-5401-5406; 5413 & 5419 For the purposes of the Kansas statutes on first degree murder, second degree murder, capital murder, voluntary manslaughter, involuntary manslaughter, and vehicular homicide, "'person" and "human being" also mean an unborn child." Section 5419 does not apply to " (1) Any act committed by the mother of the unborn child; (2) any medical procedure, including abortion, performed by a physician or other licensed medical professional at the request of the pregnant woman or her legal guardian; or (3) the lawful dispensation or administration of lawfully prescribed medication."	KAN. STAT. ANN. § 21-5601 "Endangering a child is knowingly and unreasonably permitting a child under the age of 18 years to be placed in a situation in which the child's life, body, or health may be endangered." KAN. STAT. ANN. § 21-5602 Child abuse includes causing "great bodily harm [or] disability." KAN. STAT. ANN. § 38-2202 Child neglect "means acts or omissions by a parent, guardian or person responsible for the care of a child resulting in harm to a child or presenting a likelihood of harm, that are not solely due to financial inability. . . . .Neglect . . .

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	KAN. STAT. ANN. § 65-67a06 (b) "No person shall offer or accept any valuable consideration for the fetal organs or tissue resulting from an abortion. Nothing in this subsection shall prohibit . . . payment for a pathological examination, autopsy or postmortem examination of the fetal remains."	"As used in this section, "[f]ertilization" means the fusion of a human spermatozoon with a human ovum." "Nothing in this section shall be construed as creating a cause of action against a woman for indirectly harming her unborn child by failing to properly care for herself or by failing to follow any particular program of prenatal care."		include[s] . . . failure to use resources available to treat a diagnosed medical condition if such treatment will make a child substantially more comfortable, reduce pain and suffering, or correct or substantially diminish a crippling condition from worsening."
Kentucky	None found	KY. REV. STAT. ANN. § 311.710-820. "'Fetus" means a human being from fertilization until birth. . . . "Human being" means any member of the species homo sapiens from fertilization until death."	KY. REV. STAT. ANN. § 507A.020 "A person is guilty of fetal homicide in the first degree" when they intentionally "cause the death of an unborn child. . . . Including . . . the operation of a motor vehicle under circumstances manifesting extreme indifference to human life."	KY. REV. STAT. ANN. § 600.020 An "abused or neglected child" is one whose health or welfare is harmed or threatened with harm." "Child" means any person under 18. KY. REV. STAT. ANN. 214.160 Allows for blood testing of pregnant women and newborns "to determine

				whether there is evidence of" exposure to "alcohol, a controlled substance, or a substance identified on the list provided by the Cabinet for Health and Family Services, if the attending person has reason to believe, based on a medical assessment of the mother or the infant, that the mother used any such substance for a nonmedical purpose during the pregnancy. . . [A]ny positive toxicology finding shall be evaluated . . . for abuse or neglect. . ."
Louisiana	La. Stat. Ann. § 14:87.2 "Human experimentation is the use of any infant who is born alive . . . for any scientific or laboratory research or any other kind of experimentation or study except to protect or preserve the life and health of the live born human being, or the conduct, on a human embryo or fetus in utero, of any experimentation or study except to preserve the life or to improve the health of the human embryo or fetus."	La. Stat. Ann. - Civ. Code Art. 26 "An unborn child shall be considered as a natural person for whatever relates to its interests from the moment of conception. If the child is born dead, it shall be considered never to have existed as a person, except for purposes of actions resulting from its wrongful death."	La. Stat. Ann. § 14:32.5 Feticide is defined as "the killing of an unborn child by the act, procurement, or culpable omission of a person other than the mother of the unborn child." "The offense of feticide shall not include acts which cause the death of an unborn child if those acts were committed during any abortion to which the pregnant woman or her legal guardian has consented or which was performed in an emergency as defined in R.S. 40:1061.23. Nor shall the offense	La. Stat. Ann. - Child. Code Art. 603(2), (6) (18), (24) "'"Abuse" means . . . acts that seriously endanger the physical, mental, or emotional health, welfare, and safety of the child." "'"Child" means a person under eighteen years of age." "'"Neglect" means the refusal or unreasonable failure of a parent or caretaker to supply the child with necessary

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	"Whoever commits the crime of human experimentation on an infant born alive shall be imprisoned at hard labor for not less than five nor more than twenty years, or fined not more than ten thousand dollars, or both."	LA. STAT. ANN. § 40:1061.1.2(2)(a) Under Louisiana's Pain-Capable Unborn Child Protection Act, "it is the purpose of the state to assert a compelling state interest in protecting the lives of unborn children from the stage at which substantial medical evidence indicates that they are capable of feeling pain. . . . "Unborn child" or "fetus" each mean an individual organism of the species homo sapiens from fertilization until live birth."	of feticide include acts which are "committed pursuant to usual and customary standards of medical practice during diagnostic testing or therapeutic treatment."	food, clothing, shelter, care, treatment, or counseling for any injury, illness, or condition of the child, as a result of which the child's physical, mental, or emotional health, welfare, and safety is substantially threatened or impaired. Neglect includes prenatal neglect." "'Prenatal Neglect" means exposure to chronic or severe use of alcohol or the unlawful use of any controlled dangerous substance. . .or in a manner not lawfully prescribed, which results in symptoms of withdrawal in the newborn or the presence of a controlled substance or a metabolic thereof in his body, blood, urine, or meconium that is not the result of medical treatment, or observable and harmful effects in his physical appearance or functioning."

Maine	ME. REV. STAT. tit. 22, § 1593 "1. Prohibition. A person may not use, transfer, distribute or give away a live human fetus, whether intrauterine or extrauterine, or any product of conception considered live born, for scientific experimentation or for any form of experimentation. 2. Consenting, aiding or assisting. A person may not consent to violating subsection 1 or aid or assist another in violating subsection 1."	None found	None found	ME. REV. STAT. tit. 22, § 4002 "'Abuse or neglect" means a threat to a child's health or welfare by physical, mental or emotional injury or impairment, sexual abuse or exploitation . . . or deprivation of essential needs." "Child" is defined as any person under 18. ME. REV. STAT. tit. 22, § 4004-B The state shall "act to protect infants born identified as being affected by substance use or withdrawal symptoms resulting from prenatal drug exposure, whether the prenatal exposure was to legal or illegal drugs, or having a fetal alcohol spectrum disorder, regardless of whether the infant is abused or neglected."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Maryland	None found	None found	Md. Code Ann., Crim. Law § 2-103 "A prosecution may be instituted for murder or manslaughter of a viable fetus," if the person prosecuted "intended to cause the death of the viable fetus, intended to cause serious physical injury to the viable fetus, or wantonly or recklessly disregarded the likelihood that the person's actions would cause the death of or serious physical injury to the viable fetus." "Nothing in this section applies to or infringes on a woman's right to terminate a pregnancy;. . . subjects a physician or other licensed medical professional to liability for fetal death that occurs in the course of administering lawful medical care; applies to an act or failure to act of a pregnant woman with regard to her own fetus; shall be construed to confer personhood or any rights on the fetus."	Md. Code Ann., Fam. Law § 5-701 "'Abuse" means the physical or mental injury of a child under circumstances that indicate that the child's health or welfare is harmed or at substantial risk of being harmed." "Child" is defined as any individual under 18.

Massachusetts	Mass. Gen. Laws Ann. ch. 112, § 12J Massachusetts prohibits scientific experimentation on live human fetuses, with certain exceptions. (a) "No person shall use any live human fetus whether before or after expulsion from its mother's womb, for scientific, laboratory, research or other experimentation. This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother's womb or a neonate; provided that in the best medical judgment of the physician, made at the time of the study, the procedures do not substantially jeopardize the life or health of the fetus or neonate; and provided further that, in the case of a fetus, the fetus is not the subject of a planned abortion. In any criminal proceeding, a fetus shall be conclusively presumed not to be the subject of a planned abortion if the mother signed a written statement at the time of the study, that she was not planning an abortion."	None found	*Commonwealth v. Ronchi*, 202 N.E.3d 499 (Mass. 2023) (holding that the death of a viable fetus resulting from homicide of pregnant woman is homicide even if the fetus was not directly injured) *Commonwealth v. Lawrence*, 536 N.E.2d 571 (Mass. 1989) (extending liability for death of a viable fetus to charge of involuntary manslaughter) *Commonwealth v. Cass*, 467 N.E.2d 1324 (Mass. 1984) (holding that a viable fetus is a person for vehicular homicide statute).	Mass. Gen. Laws Ann. ch. 265, § 13L "Child" is defined as any person under 18. Under the Criminal Code, "whoever wantonly or recklessly engages in conduct that creates a substantial risk of serious bodily injury. . . to a child . . . shall be punished by imprisonment."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	This provision does "not prohibit or regulate diagnostic or remedial procedures the purpose of which is: (i) to determine the life or health of the fetus or neonate involved; (ii) to preserve the life or health of the fetus or neonate involved or the mother involved; (iii) to improve the chances of a viable birth for a fetus with a congenital or other fetal conditions that would otherwise substantially impair or jeopardize the fetus's health or viability; or (iv) research approved by an institutional review board applying federal regulations for the protection of fetuses and neonates, that are conducted for the purpose of developing, comparing or improving diagnostic or therapeutic fetal or neonatal interventions to improve the viability or quality of life of fetuses, neonates and children."			

	A fetus is a live fetus "when, in the best medical judgment of a physician, it shows evidence of life as determined by the same medical standards as are used in determining evidence of life in a spontaneously-aborted fetus at approximately the same stage of gestational development."			
Michigan	MICH. COMP. LAWS ANN. § 333.2685 "A person shall not use a live human embryo, fetus, or neonate for 'nontherapeutic research' if, in the best judgment of the person conducting the research, based upon the available knowledge or information at the approximate time of the research, the research substantially jeopardizes the life or health of the embryo, fetus, or neonate. Nontherapeutic research shall not in any case be performed on an embryo or fetus known by the person conducting the research to be the subject	None found	MICH. COMP. LAWS ANN. § 750.322 "The willful killing of an unborn quick child by any injury to the mother of such child, which would be murder if it resulted in the death of such mother, shall be deemed manslaughter." MICH. COMP. LAWS ANN. § 600.2922a "A person who commits a wrongful or negligent act against a pregnant individual is liable for damages if the act results in a miscarriage or stillbirth by that individual, or physical injury to or the death of the embryo or fetus. . . . This section does not apply to . . . (a) An act committed by the pregnant individual,	MICH. COMP. LAWS ANN. § 750.136b "A person is guilty of child abuse in the first degree if the person knowingly or intentionally causes serious physical harm or serious mental harm to a child." "Child" is defined as a "person who is less than eighteen years of age." *People v. Jones*, 317 Mich. App. 416, 894 N.W.2d 723 (Mich. Ct. App. 2016) (holding that "a fetus is not a child for purposes of . . . the child abuse statute" and that the statute therefore does not reach prenatal drug use).

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TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	of a planned abortion being performed for any purpose other than to protect the life of the mother." MICH. COMP. LAWS ANN. § 333.2692 The term "nontherapeutic research" means "scientific or laboratory research, or other kind of experimentation or investigation not designed to improve the health of the research subject." MICH. COMP. LAWS ANN. § 333.2688(1 "Research may not knowingly be performed upon a dead embryo, fetus, or neonate unless the consent of the mother has first been obtained."		(b) A medical procedure performed by a physician or other licensed health professional within the scope of his or her practice and with the pregnant individual's consent or the consent of an individual who may lawfully provide consent on her behalf or without consent as necessitated by a medical emergency. . . . (c) The lawful dispensation, administration, or prescription of medication."	

Minnesota	MINN. STAT. ANN. § 145.421- 145.422 "Human conceptus" is defined as "any human organism, conceived either in the human body or produced in an artificial environment other than the human body, from fertilization through the first 265 days thereafter." "Subdivision 1. Penalty. Whoever uses or permits the use of a living human conceptus for any type of scientific, laboratory research or other experimentation except to protect the life or health of the conceptus, or except as herein provided, shall be guilty of a gross misdemeanor. Subd. 2. Permitted acts. The use of a living human conceptus for research or experimentation which verifiable scientific evidence has shown to be harmless to the conceptus shall be permitted."	None found	MINN. STAT. ANN. §§609.266, 609.2661- 609.2665, 609.268(1) A person who "causes the death of an unborn child" at any stage of pre-natal development is guilty of murder or manslaughter of varying degrees. MINN. STAT. ANN. §609.2114 "A person is guilty of criminal vehicular operation resulting in death to an unborn child . . .if the person causes the death of an unborn child as a result of operating a motor vehicle: (1) in a grossly negligent manner; (2) in a negligent manner while under the influence of: . . . alcohol . . . a controlled substance . . . a cannabis product. . .any combination of those elements;" or [driving] "in a negligent manner while under the influence of an intoxicating substance."	MINN. STAT. ANN. § 609.378 A parent is guilty of child neglect if they "willfully deprive a child . . . of healthcare . . . when the deprivation harms or is likely to harm the child's physical, mental, or emotional health." "Child" is defined as any person under 18.

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TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	Minn. Stat. Ann. § 137.47 "A researcher at the University of Minnesota must obtain approval from the ["Fetal Tissue Research Committee" or "FTR"] before conducting research using fetal tissue. The FTR must consider whether alternatives to fetal tissue would be sufficient for the research. If the proposed research involves aborted fetal tissue, the researcher must provide a written narrative justifying the use of aborted fetal tissue and discussing whether alternatives to aborted fetal tissue, including non-aborted fetal tissue, can be used."			
Mississippi	None found	Mississippi includes fetal personhood language throughout its abortion laws. Miss. Code Ann. § 41-41-191 Miss. Code Ann. § 41-41-405	Miss. Code Ann. § 97-3-37 For purposes of criminal offenses against the person, "the term 'human being' includes an unborn child at every stage of gestation from conception until live birth, and the term 'unborn child'	Miss. Code Ann. § 43-21-105 "'Abused child" means a child whose parent, guardian, or custodian . . . has caused or allowed to be caused upon the child . . . non-accidental physical injury or other maltreatment."

"'Human being" means an individual member of the species Homo sapiens, from and after the point of conception."

means a member of the species homo sapiens, at any stage of development, who is carried in the womb."

"'Neglected child" means a child whose parent, guardian, or custodian . . . neglects or refuses . . . to provide . . . proper and necessary care or support . . . or medical, surgical, or other care necessary for his well-being."

A "child" is a person who has not reached his eighteenth birthday.

Miss. Code Ann. § 97-5-39 (4)(a)

A parent is guilty of child endangerment if they "knowingly cause[] or permit[] the child to be present where any person is selling, manufacturing, or possessing immediate precursors or chemical substances with intent to manufacture, sell or possess a controlled substance."

A 2007 opinion by the Mississippi Attorney General states that this provision of the statute is "referencing a child living outside his mother's womb" and "does not apply to an unborn child being present in the mother's womb." 2007 WL 1725165; Miss. A.G. Op. 2007-00182 (Apr. 16, 2007)

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Missouri	Mo. Ann. Stat. § 188.037 Under Missouri law, "no person shall use any fetus or child aborted alive for any type of scientific, research, laboratory or other kind of experimentation either prior to or subsequent to any abortion procedure except as necessary to protect or preserve the life and health of such fetus or child aborted alive."	Mo. Ann. Stat. § 1.205 "1. The general assembly of this state finds that: (1) The life of each human being begins at conception; (2) Unborn children have protectable interests in life, health, and well-being; (3) The natural parents of unborn children have protectable interests in the life, health, and well-being of their unborn child. 2. Effective January 1, 1988, the laws of this state shall be interpreted and construed to acknowledge on behalf of the unborn child at every stage of development, all the rights, privileges, and immunities available to other persons, citizens, and residents of this state, subject only to the Constitution of the United States, and decisional interpretations thereof by the United States Supreme Court and specific provisions to the contrary in the statutes and constitution of this state.	Mo. Ann. Stat. § 565.300 "3. A person commits the offense of infanticide if he or she causes the death of a living infant with the purpose to cause said death by an overt act performed when the infant is partially born or born. . . . 5. A physician using procedures consistent with the usual and customary standards of medical practice to save the life of the mother during pregnancy or birth or to save the life of any unborn or partially born child of the same pregnancy shall not be criminally responsible under this section. In no event shall the mother be criminally responsible pursuant to this section for the acts of the physician if the physician is not held criminally responsible pursuant to this section. 6. This section shall not apply to any person who performs or attempts to perform a legal abortion if the act that causes the death is performed prior to the child being partially born, even though the death of the child occurs as a result of the abortion after the child is partially born."	Mo. Ann. Stat. § 568.060 "'Abuse" [is] the infliction of physical, sexual, or mental injury against a child by any person eighteen years of age or older. " Mo. Ann. Stat. § 568.045 -050 "A person commits the offense of endangering the welfare of a child in the first degree if he or she . . . [k]nowingly acts in a manner that creates a substantial risk to the life, body, or health of a child less than seventeen years of age" and "in the second degree if he or she . . . [w]ith criminal negligence acts in a manner that creates a substantial risk to the life, body or health of a child less than seventeen years of age."

3. As used in this section, the term "unborn children" or "unborn child" shall include all unborn child or children or the offspring of human beings from the moment of conception until birth at every stage of biological development.

4. Nothing in this section shall be interpreted as creating a cause of action against a woman for indirectly harming her unborn child by failing to properly care for herself or by failing to follow any particular program of prenatal care."

Mo. Ann. Stat. § 188.010(1)

"[I]t is the intention of the general assembly of the state of Missouri to: (1) Defend the right to life of all humans, born and unborn. . . ."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Montana	None found	MONT. CODE ANN. § 41-1-103 "A child conceived but not yet born is an existing person, so far as may be necessary for its interests in the event of its subsequent birth."	MONT. CODE ANN. § 45-5-102 "(1) A person commits the offense of deliberate homicide if . . . (c) the person purposely or knowingly causes the death of a fetus of another with knowledge that the woman is pregnant." MONT. CODE ANN. § 45-5-116 Under the homicide statutes, "'fetus' means an organism of the species Homo sapiens from 8 weeks of development until complete expulsion or extraction from a woman's body." A deliberate homicide charge "may not be brought against: (a) a person for conduct relating to an abortion for which the consent of the pregnant woman or a person authorized by law to act on her behalf has been obtained or for which the consent is implied by law; (b) a person for any medical treatment of the pregnant woman or her fetus; or (c) a woman with respect to her fetus."	MONT. CODE ANN. § 41-3-102 "(7)(a) "Child abuse or neglect" means (i) actual physical or psychological harm to a child; [or] (ii) substantial risk of physical or psychological harm to a child by the acts or omissions of a person responsible for the child's welfare. "(6) "Child" . . .means any person under 18 years of age."

Nebraska	None found	None found	NEB. REV. STAT. ANN. § 28-391(1) "A person commits murder of an unborn child in the first degree if he or she in committing an act or engaging in conduct that causes the death of an unborn child, intends, with deliberate and premeditated malice, to kill the unborn child or the mother of the unborn child with knowledge of the pregnancy."	NEB. REV. STAT. ANN. § 28-707 " A person commits child abuse if he or she knowingly, intentionally, or negligently causes or permits a minor child to be . . . [p]laced in a situation that endangers his or her life or physical or mental health. . ."
Nevada	None found	None found	NEB. REV. STAT. ANN. § 200.210 "A person who willfully kills an unborn quick child, by any injury committed upon the mother of the child, commits manslaughter and shall be punished for a category B felony. . . ."	NEB. REV. STAT. ANN. § 432B.020 "Abuse or neglect of a child means [p]hysical or mental injury of a nonaccidental nature" or "[n]egligent treatment or maltreatment" of a child" caused or allowed by a person responsible for the welfare of the child. . ." NEB. REV. STAT. ANN. § 432B.040 "Child" is defined as any person under 18. *Sheriff v. Encoe,* 885 P.2d 596 (Nev. 1994) (holding that the child endangerment statute "does not apply to pregnant woman's ingestion of illegal substances and resulting transmission of these substances to child through the umbilical cord").

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TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
New Hampshire	None found	None found	N.H. REV. STAT. § 630:1-a Under the state's homicide statutes, "the meaning of "another" shall include a fetus" except the homicide statutes do not "apply to (1) Any act committed by the pregnant woman; (2) Any act committed at the request or direction of the pregnant women or for the benefit of the pregnant woman; (3) Any act performed by a physician or other medical professional in the course of such physicians' or medical professional's professional duties; or (4) Any act taken in furtherance of the lawful dispensation or administration of prescription or nonprescription medication. . . . "Fetus" means an unborn offspring, from the embryo stage which is the end of the twentieth week after conception or, in the case of in vitro fertilization, the end of the twentieth week after implantation, until birth."	N.H. REV. STAT. ANN. § 169-C:3 Under New Hampshire's Child Protection Act, "'[c]hild' means any person who has not reached his eighteenth birthday." The definition of ""abused child" means any child who has been . . . intentionally physically injured; or . . . [p]hysically injured by other than accidental means."

New Jersey	None found	None found	N.J. STAT. ANN. § 2C:11-2 *State in Interest of A.W.S.*, 440 A.2d 1144 (N.J. Super. App. Div. 1981) (holding that an unborn fetus is not a "human being" within meaning of criminal homicide provision of Code of Criminal Justice).	N.J. STAT. ANN. § 9:6-1 "Cruelty to a child shall consist in any of the following acts: . . . (b) inflicting upon a child unnecessary suffering or pain, either mental or physical; . . . (d) any willful act of omission or commission whereby unnecessary suffering or pain, either mental or physical, is caused or permitted to be inflicted on a child; (e) or exposing a child to unnecessary hardship, fatigue or mental or physical strains that may tend to injure the health or physical or moral well-being of such child." *NJ Division of Youth & Family Services v. L.V.*, 889 A.2d 1153 (Ch. Div. 2005) (recognizing that the right of a mother to make decisions about what medications she will take during her pregnancy is part of her constitutional right to privacy and left solely to her discretion, and holding that the refusal by HIV+ mother to take recommended medication during pregnancy

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
				to reduce risk of transferring the virus to fetus did not constitute act of abuse or neglect because mother had constitutional right to refuse such treatment, even at risk to unborn child).
New Mexico	N.M. STAT. ANN. § 24-9A-2 "A. No woman, known to be pregnant according to generally accepted medical standards, shall be involved as a subject in any clinical research activity unless: (1) the purpose of the activity is to meet the health needs of the mother or the fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or (2) there is no significant risk to the fetus. B. An activity permitted under Subsection A of this section may be conducted only if the mother is legally	None found	None found	N.M. STAT. ANN. § 30-6-1 Child "means a person who is less than eighteen years of age. . . ." "Abuse of a child consists of a person knowingly, intentionally, or negligently, and without justifiable cause, causing or permitting a child to be: placed in a situation that may endanger the child's life or health. . . ." *State v. Mondragon,* 203 P.3d 105 (N.M. Ct. App. 2008) (holding that fetus is not a child for purposes of child abuse statute, and finding infliction of injuries on a fetus insufficient to support

competent and has given her informed consent after having been fully informed of the possible impact on fetus."

N.M. STAT. ANN. § 24-9A-3

"A. No fetus shall be involved as a subject in any clinical research activity unless the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs or no significant risk to the fetus is imposed by the research activity.
B. An activity permitted under Subsection A of this section shall be conducted only if the mother is legally competent and has given her informed consent."

N.M. STAT. ANN. § 24-9A-5

"A. No clinical research activity involving fetuses, live-born infants or pregnant women shall be conducted unless:
(1) appropriate studies on animals and nonpregnant human beings have been completed;

a charge of child abuse resulting in death, even though the death occurred after mother gave birth to a live child).

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	(2) anyone engaged in conducting the research activity will have no part in: (a) any decisions as to the timing, method and procedures used to terminate the pregnancy; and (b) determining the viability of the fetus at the termination of the pregnancy; and (3) no procedural changes which may cause significant risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the research activity. B. No inducements, monetary or otherwise, shall be offered to any woman to terminate her pregnancy for the purpose of subjecting her fetus or live-born infant to clinical research activity.			

C. No consent to involve a pregnant woman, fetus or infant as a subject in clinical research activity shall be valid unless the pregnant woman or the parent or guardian of the infant has been fully informed of the following:
(1) a fair explanation of the procedures to be followed and their purposes, including identification of any procedures which are experimental;
(2) a description of any attendant discomforts and risks reasonably to be expected;
(3) a description of any benefits reasonably to be expected; (4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;
(5) an offer to answer any inquiries concerning the procedure; and
(6) an instruction that the person who gave the consent is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
New York	None found	None found	N.Y. Penal Law §125.00 NY's homicide laws do not include a specific statutory provision for fetal homicide.	N.Y. Penal Law § 260.10 "A person is guilty of endangering the welfare of a child when: . . . He or she knowingly acts in a way likely to harm the physical, mental, or moral welfare of child less than seventeen years of age. . . ." *People v. Morabito,* 580 N.Y.S 843 (City Ct. 1992) (holding that an unborn child does not constitute a "child" under the child endangerment statute in case where mother ingested cocaine while pregnant).
North Carolina	None found	None found	N.C. Gen. Stat. Ann. § 14-23.2. "(a) A person who unlawfully causes the death of an unborn child is guilty of the separate offense of murder of an unborn child if the person does any one of the following: (1) Willfully and maliciously commits an act with the intent to cause the death of the unborn child.	N.C. Gen. Stat. Ann. § 14-318.4 "Child abuse" includes a "parent or other person providing care to or supervision of a child less than 16 years of age who intentionally inflicts any serious physical injury upon or to the child" or "whose willful act or grossly negligent omission in the care of the child shows a reckless disregard for human life."

			(2) Causes the death of the unborn child in perpetration or attempted perpetration of murder in the any of the criminal offenses set forth under G.S. 14-17 [murder in the first or second degree]. (3) Commits an act causing the death of the unborn child that is inherently dangerous to human life and is done so recklessly and wantonly that it reflects disregard of life."	
North Dakota	N.D. Cent. Code Ann. § 14-02.2-01 "A person may not use any live human fetus, whether before or after expulsion from its mother's womb, for scientific, laboratory, research, or other kind of experimentation. This section does not prohibit procedures incident to the study of a human fetus while it is in its mother's womb, provided that in the best medical judgment of the physician, made at the time of the study, the procedures do not substantially jeopardize the life or health of the fetus,	N.D. Cent. Code Ann. § 14-10-15 "A child conceived but not born is to be deemed an existing person so far as may be necessary for its interests in the event of its subsequent birth." *Hopkins v. McBane*, 359 N.W.2d 862 (N.D. 1984) (holding that the stillbirth of a viable child constitutes "death of a person" for purposes of applying the wrongful death statute).	N.D. Cent. Code § 12.1-17.1-02 "1. A person is guilty of murder of an unborn child, a class AA felony, if the person: a. Intentionally or knowingly causes the death of an unborn child; b. Causes the death of an unborn child under circumstances manifesting extreme indifference to the value of the life of the unborn child or the pregnant woman;. . ."	N.D. Cent. Code Ann. § 19-03.1-22.2 "1.b. "Child" means an individual who is under the age of eighteen years. . . . 2. . . .[A] person who knowingly or intentionally causes or permits a child. . . to be exposed to, to ingest or inhale, or to have contact with a controlled substance, chemical substance, or drug paraphernalia . . . is guilty of a Class C felony. . . ." *State v. Stegull*, 828 N.W.2d 526 (N.D. 2015) (holding that an unborn fetus was not a "child" within meaning of endangerment of child,

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	and provided the fetus is not the subject of a planned abortion. In any criminal proceeding the fetus is conclusively presumed not to be the subject of a planned abortion if the mother signed a written statement at the time of the study, that the mother was not planning an abortion." N.D CENT. CODE ANN. § 14-02.2-02 "An experimentation may not knowingly be performed upon a dead fetus resulting from an occurrence other than an induced abortion unless the consent of the mother has first been obtained; provided, however, that the consent is not required in the case of a routine pathological study. In any criminal proceeding, consent is conclusively presumed			and thus, defendant was not criminally liable for harm to fetus, later born alive, from ingestion of methamphetamine while pregnant). *State v. Geiser*, 763 N.W.2d 469 (N.D. 2009) (holding that an unborn child is not a "child" under the statute defining crime of endangerment of a child or vulnerable adult).

to have been granted for the purposes of this section by a written statement, signed by the mother who is at least eighteen years of age, to the effect that she consents to the use of her fetus for scientific, laboratory, research, or other kind of experimentation or study. Such written consent constitutes lawful authorization for the transfer of the dead fetus . . . A person may not use a fetus or fetal organs or tissue resulting from an induced abortion in animal or human research, experimentation, or study, or for animal or human transplantation except for diagnostic or remedial procedures, the purpose of which is to determine the life or health of the fetus or to preserve the life or health of the fetus or mother, or pathological study. . . For purposes of this section, the word "fetus" includes also an embryo or neonate."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Ohio	None found	Ohio Rev. Code Ann. § 2901.01 Ohio's criminal code, with some exceptions, defines "person" as including an "unborn human who is viable" which is further defined as follows: "(B)(1)(c)(i) "Unborn human" means an individual organism of the species Homo sapiens from fertilization until live birth. (ii) "Viable" means the stage of development of a human fetus at which there is a realistic possibility of maintaining and nourishing of a life outside the womb with or without temporary artificial life-sustaining support."	Ohio Rev. Code Ann. § 2901.01 (B)(1)(a)(ii) "Person" is defined in the state's homicide offenses as including an "unborn human who is viable." Ohio Rev. Code Ann. § 2903.09 ""Unlawful termination of another's pregnancy" means causing the death of an unborn member of the species homo sapiens, who is or was carried in the womb of another, as a result of injuries inflicted during the period that begins with fertilization and that continues unless and until live birth occurs. . . ." This definition shall not be "construed as prohibiting any pregnant woman or her physician from performing an abortion with the actual consent of the pregnant woman, with the consent of the pregnant woman implied by law in a medical emergency, or with the approval of one otherwise authorized by law to consent to medical treatment on behalf of the pregnant woman."	Ohio Rev. Code Ann. § 2925.02(A)(5) "No person shall knowingly . . . [b]y any means, furnish or administer a controlled substance to a pregnant woman or induce or cause a pregnant woman to use a controlled substance, when the offender knows that the women is pregnant or is reckless in that regard." Ohio Rev. Code Ann. § 2919.22 (A) "No person, who is the parent . . . of a child under eighteen years of age . . . shall create a substantial risk to the health or safety of the child, by violating a duty of care, protection, or support." *State v. Gray*, 584 N.E.2d 710 (Ohio 1991) (holding that a parent may not be prosecuted for child endangerment under 2919.22(A) for substance abuse occurring before the birth of the child).

				Ohio Rev. Code Ann. § 2151.031 "[A]n "abused child" includes any child who. . . is endangered. . . .[or] [e]xhibits evidence of any physical or mental injuries or death, inflicted by other than accidental means. . . ." *In re Ruiz*, 500 N.E.2d 935 (Ohio Com. Pl. 1986) (stating that the definition of "abused child" includes a viable unborn child for purposes of the statute).
Oklahoma	None found	None found	Okla. Stat. Ann. tit. 21 § 691 "A. "Homicide" is the killing of one human being by another." B. . . . "Human being" includes an unborn child [as defined in Oklahoma abortion statutes]. C. Homicide shall not include: . . . . 2. Acts which are committed pursuant to the usual and customary standards of medical practice during diagnostic testing or therapeutic treatment. . . . D. Under no circumstances shall the mother of the unborn child be prosecuted for causing the death of the unborn child unless the mother has committed a crime that caused the death of the unborn child."	Okla. Stat. Ann. tit. 21, § 843.5 "Child neglect" means the "willful or malicious neglect . . . of a child under eighteen (18) years of age by a person responsible for a child's health, safety or welfare." *State v. Allen*, 492 P.3d 27 (Okla. Crim. App. 2021) (holding that an unborn child constitutes a "child" for purposes of child neglect statute in case where mother ingested methamphetamine while pregnant).

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Oregon	None found	None found	Or. Rev. Stat. Ann. §163.005 "Human being" in the homicide statute is defined as a "person who has been born and was alive at the time of the criminal act."	Or. Rev. Stat. Ann. § 12.117 (2) . . ."[C]hild abuse" means any of the following: (a) Intentional conduct by an adult that results in: (A) Any physical injury to a child; or (B) Any mental injury to a child which results in observable and substantial impairment of the child's mental or psychological ability to function caused by cruelty to the child. . . . Or. Rev. Stat. Ann. § 475.910 ". . .[I]t is unlawful for any person to intentionally apply a controlled substance to the body of another person by injection, inhalation, ingestion or any other means if the other person is under age 18 years of age." *Oregon v. Cervantes*, 223 P.3d 425 (Or. App. 2009) (holding that a mother's ingestion of methamphetamine while pregnant did not cause reckless endangerment to "another person" because a fetus not yet born is not a person).

Pennsylvania	18 Pa. Stat. And Cons. Stat. Ann. § 3216 "(a) Any person who knowingly performs any type of nontherapeutic experimentation or nontherapeutic medical procedure (except an abortion as defined in this chapter) upon any unborn child, or upon any child born alive during the course of an abortion, commits a felony. . . "Nontherapeutic" means that which is not intended to preserve the life or health of the child upon whom it is performed.". . . "No fetal tissue or organs may be procured or used without the written consent of the mother. No consideration of any kind for such consent may be offered or given. Further, if the tissue or organs are being derived from abortion, such consent shall be valid only if obtained after the decision to abort has been made". . .	18 Pa. Stat. And Cons. Stat. Ann. § 3202 "(c) In every relevant civil or criminal proceeding in which it is possible to do so without violating the Federal Constitution, the common and statutory law of Pennsylvania shall be construed so as to extend to the unborn the equal protection of the laws and to further the public policy of this Commonwealth encouraging childbirth over abortion."	18 Pa. Stat. and Cons. Stat. Ann. § 2603 "An individual commits criminal homicide of an unborn child if the individual intentionally, knowingly, recklessly or negligently causes the death of an unborn child in violation of section 2604 (relating to murder of unborn child) or 2605 (relating to voluntary manslaughter of unborn child)."	23 Pa. Stat. and Cons. Stat. Ann. § 6303 "Child" is defined in PA Child Protective Services Law child as "[a]n individual under 18 years of age." *Interest of L.J.B.*, 199 A.3d 868 (Pa. 2018) (holding that "child," as defined by the statute, does not include a fetus or unborn child, and mother was not perpetrator of child abuse for using opioids while pregnant).

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	"All persons who participate in the procurement, use or transplantation of fetal tissue or organs . . . shall be informed as to whether the particular tissue or organ involved was procured as a result of either: (i) stillbirth; (ii) miscarriage; (iii) ectopic pregnancy; (iv) abortion; or (v) any other means. . . (c) Nothing in this section shall be construed to condone or prohibit the performance of diagnostic tests while the unborn child is in utero. . ."			
Rhode Island	R.I. GEN. LAWS ANN. § 11-54-1 "(a) No person shall use any live human fetus, whether before or after expulsion from its mother's womb, for scientific, laboratory research, or other kind of experimentation.	None found	None found	40 R.I. GEN. LAWS ANN. § 40-11-2 "(1) "Abused or neglected child" means a child whose physical or mental health or welfare is harmed, or threatened with harm, when his or her parent or other person responsible

This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother's womb, provided that in the best medical judgment of the physician, made at the time of the study, the procedures do not substantially jeopardize the life or health of the fetus, and provided the fetus is not the subject of a planned abortion. In any criminal proceeding the fetus shall be conclusively presumed not to be the subject of a planned abortion if the mother signed a written statement at the time of the study that she was not planning an abortion.". . .

"(b) This section shall not prohibit or regulate diagnostic or remedial procedures, the purpose of which is to determine or to preserve the life or health of the fetus involved or the mother involved."

for his or her welfare: "[i]nflicts, or allows to be inflicted, upon the child physical or mental injury . . . or . . . [c]reates, or allows to be created, a substantial risk of physical or mental injury to the child."

(2) "Child" means a person under the age of . . .18."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
	"No experimentation may knowingly be performed upon a dead fetus unless the consent of its mother has first been obtained, provided, that such consent shall not be required in the case of a routine pathological study. In any criminal proceeding, consent shall be conclusively presumed to have been granted for the purposes of this section by a written statement, signed by the mother, who is at least eighteen (18) years of age, to the effect that she consents to the use of her fetus for scientific, laboratory, research, or other kind of experimentation or study; that written consent shall constitute lawful authorization for the transfer of the dead fetus."			

South Carolina	None found	None found	S.C. Code Ann. § 16-3-1083 "(A)(1) A person who commits a violent crime . . . that causes the death of, or bodily injury to, a child who is in utero at the time that the violent crime was committed, is guilty of a separate offense. . . . (2)(a) the punishment for a separate offense . . . is the same as the punishment provided for that criminal offense had the death or bodily injury occurred to the unborn child's mother. (B) Nothing in this section may be construed to permit the prosecution under this section: (1) of a person for conduct relating to an abortion for which the consent of the pregnant woman, or a person authorized by law to act on her behalf, has been obtained or for which such consent is implied by law; (2) of a person for any medical treatment of the pregnant woman or her unborn child; or (3) of a woman with respect to her unborn child." (C) . . . [T]he term "unborn child" means a "child in utero," and the term "child in utero" or "child who is in utero" means a member of the species homo sapiens, at any stage of development, who is carried in the womb."	S.C. Code Ann. § 63-5-70 "(A) It is unlawful for a person who has charge or custody of a child, or who is the parent or guardian of a child, or who is responsible for the welfare of a child [as defined in the statute] to: (1) place the child at unreasonable risk of harm affecting the child's life, physical or mental health, or safety; (2) do or cause to be done unlawfully or maliciously any bodily harm to the child so that the life or health of the child is endangered or likely to be endangered." *Whitner v. State*, S.E.2d 777 (S.C. 1997) (holding that a viable fetus is a "child" within meaning of child abuse and endangerment statute, and mother could be charged under statute for ingesting crack cocaine during third trimester of pregnancy, causing baby to be born with cocaine metabolites in its system).

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
South Dakota	S.D. Codified Laws § 34-14-17 "No person may knowingly conduct nontherapeutic research that subjects a human embryo to substantial risk of injury or death. No person may sell or transfer a human embryo with the knowledge that the embryo will be subjected to nontherapeutic research."	S.D. Codified Laws § 21-5-1 *Wiersma v. Maple Leaf Farms*, 543 N.W.2d 787 (S.D. 2002) (holding that "South Dakota's wrongful death statute . . . authorizes a remedy when a third party wrongfully ends their child's life before birth. Parents may seek redress regardless of whether their unborn child was viable").	S.D. Codified Laws § 22- 16-1 "Homicide is the killing of one human being, including an unborn child, by another." S.D. Codified Laws. § 22-16-1.1 "Homicide is fetal homicide if the person knew, or reasonably should have known, that a woman bearing an unborn child was pregnant and caused the death of the unborn child without lawful justification and if the person: (1) Intended to cause the death of or do serious bodily injury to the pregnant woman or the unborn child; or (2) Knew that the acts taken would cause death or serious bodily injury to the pregnant woman or her unborn child; or (3) If perpetrated without any design to effect death by a person engaged in the commission of any felony. . . . This section does not apply to acts which cause the death of an unborn child if those acts were committed during any abortion, lawful or unlawful, to which the pregnant woman consented."	S.D. Codified Laws § 26-8A-2 "[T]he term abused or neglected child means a child . . . (6) Who is threatened with substantial harm; [or] (9) Who was subject to prenatal exposure to abusive use of alcohol, marijuana, or any controlled drug/ substance not lawfully prescribed by a practitioner. . ." S.D. Codified Laws § 26-1-2 "A child conceived, but not born, is to be deemed an existing person so far as may be necessary for its interests in the event of its subsequent birth."

Tennessee	TENN. CODE ANN. § 39-15-208 "It is unlawful for any person, agency, corporation, partnership or association to engage in medical experiments, research, or the taking of photographs upon an aborted fetus without the prior knowledge and written consent of the mother(.)"	TENN. CODE ANN. § 39-15-214 "The general assembly finds: . . . (5) At conception, a new and genetically distinct human being is formed; (6) The state has a legitimate, substantial, and compelling interest in protecting the rights of all human beings, including the fundamental and absolute right of unborn human beings to life, liberty, and all rights protected by the Fourteenth and Ninth Amendments to the United States Constitution."	TENN. CODE ANN. § 39-13-214 TN criminal homicide statutes define "another" and "another person" [to] include a human embryo or fetus at any stage of gestation in utero, when any such term refers to the victim of any act made criminal by this part . . . . [which does not] apply to "any act or omission by a pregnant woman with respect to an embryo or fetus with which she is pregnant, or to any lawful medical or surgical procedure to which a pregnant woman consents, performed by a health care professional who is licensed to perform such procedure."	TENN. CODE ANN. § 39-15-401 TN's child abuse statute criminalizes "knowingly, other than by accidental means, treat[ing] a child under eighteen (18) years of age in such a manner as to inflict injury". . .or to abuse or neglect a child "so as to adversely affect the child's health and welfare." Under a 1995 AG opinion, the term "child" does *not* include a fetus, and use of cocaine by a pregnant women cannot be considered child abuse or aggravated child abuse under this statute. Tenn. Op. Att'y. Gen. No. 95-023 (Mar. 27, 1995). TENN. CODE ANN. § 39-13-107 Tennessee's "assaultive offenses" (assault, aggravated assault, reckless endangerment) statutes that define "individuals" and "another person" to "include a human embryo or fetus at any state of gestation in utero, when any such term refers to the victim of any

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
				act made criminal under this section. . . [This does not apply] to any act or omission by a pregnant women with respect to an embryo or fetus with which she is pregnant, or to any lawful medical or surgical procedure to which a pregnant women consents, performed by a healthcare professional who is licensed to perform such procedure." A 2008 AG opinion states that "A pregnant mother who ingests an illegal drug, thereby injuring her viable fetus, can be criminally liable for assault if she intentionally, knowingly, or recklessly causes bodily injury; aggravated assault if she intentionally, knowingly, or recklessly causes serious bodily injury; or reckless endangerment if she places the fetus in imminent danger of death or serious bodily injury." Tenn. Op. Att'y Gen., No. 08-114 (May 21, 2008).

Texas	None found	Tex. Penal Code Ann. § 1.07 (26) Under the Texas Penal Code, "'Individual" means a human being who is alive, including an unborn child at every stage of gestation from fertilization to birth."	Tex. Penal Code Ann. § 1.07 Under the Texas Penal Code, ""Individual" means a human being who is alive, including "an unborn child at every stage of gestation from fertilization until birth."	Tex. Health & Safety Code Ann. § 481.122 "(a) A person commits an offense if the person knowingly delivers a controlled substance . . . to a person: (1) who is a child; . . . (d) In this section, "child" means a person younger than 18 years of age." *Ward v. State*, 188 S.W.3d 874 (Tex. App. 2006) (holding that a mother's ingestion of cocaine that entered the unborn child's body through the umbilical cord did not constitute an "actual transfer" of a controlled substance under the statute because there was no evidence that the unborn child actually "handled, touched, manipulated, or otherwise exercised physical possession over the drug"). Tex. Penal Code Ann. § 22.12 Texas' Assaultive Offenses statutes (including injuries to children and child endangerment) "does not apply to conduct charged as having been committed against . . . an unborn child if the conduct is: (1) committed

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
				by the mother of the unborn child, (2) a lawful medical procedure performed by a physician or other healthcare provider with the requisite consent, (3) a lawful medical procedure performed by a physician or other licensed health care provider with the requisite consent as part of an assisted reproduction . . ., or (4) the dispensation of a drug in accordance with law or administration of a drug prescription." TEX. PENAL CODE ANN. § 22.04 "(a) A person commits an [assaultive] offense if he intentionally, knowingly, recklessly, or with criminal negligence, by act or intentionally, knowingly, or recklessly by omission, causes to a child, . . . (1) serious bodily injury;(2) serious mental deficiency, impairment, or injury; or (3) bodily injury. . . . . (c) In this section: (1) "Child" means a person 14 years of age or younger.

Utah	Utah Code Ann. § 76-7-310 "Live unborn children may not be used for experimentation, but when advisable, in the best medical judgment of the physician, may be tested for genetic defects."	Utah Code Ann. § 76-7-301.1 (1) "It is the finding and policy of the Legislature, reflecting and reasserting the provisions of Article I, Sections 1 and 7, Utah Constitution, which recognize that life founded on inherent and inalienable rights is entitled to protection of law and due process; and that unborn children have inherent and inalienable rights that are entitled to protection by the state of Utah pursuant to the provisions of the Utah Constitution."	Utah Code Ann. § 76-5-201 "(1)(a) (ii) "Criminal homicide" means an act causing the death of another human being, including an unborn child at any stage of the unborn child's development. . . . (3)[A]n actor is not guilty of criminal homicide if: (a) the death of an unborn child is caused by an abortion; (b) the sole reason for the death of an unborn child is that the actor: (i) refused to consent to: (A) medical treatment; or (B) a cesarean section; or (ii) failed to follow medical advice; or (c) a woman causes the death of her own unborn child, and the death: (i) is caused by a criminally negligent act or reckless act of the woman; and (ii) is not caused by an intentional or knowing act of the woman."	Utah Code Ann. § 76-5-112.5 "(1)(a)(ii) "Child" means an individual who is under 18 years old." "(2) An actor commits endangerment of a child . . . if the actor knowingly or intentionally causes or permits a child . . . to be exposed to, inhale, ingest, or have contact with a controlled substance, chemical substance, or drug paraphernalia."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Vermont	None found	None found	VT. STAT. ANN. tit. 13 §2301 *State v. Oliver*, 563 A.2d 1002 (Vt. 1989) (holding that a viable fetus who is not born alive does not meet the definition of person under statute imposing criminal penalties for negligent operation of a motor vehicle that results in the death of any "person").	VT. STAT. ANN. tit. 13 §1304 "(a) A person over age 16 years of age, having the custody, charge or care of a child, who willfully assaults, ill treats, neglects, or abandons or exposes such child, or causes or procures such child to be assaulted, ill-treated, neglected, abandoned or exposed, in a manner to cause such child unnecessary suffering, or to endanger his or her health shall be imprisoned . . . or fined or both."
Virginia	VA. CODE ANN. § 32.1-162.19 "B. No human research shall be conducted or authorized by such institution or agency unless the committee has reviewed and approved the proposed human research project giving consideration to. . . (vi) when some or all of the	None found	VA. CODE ANN. § 18.2-32.2 "Any person who unlawfully, willfully, deliberately and maliciously kills the fetus of another is guilty of a felony."	VA. CODE ANN. § 18.2-371.1 "B. 1. Any parent, guardian, or other person responsible for the care of a child under the age of 18 whose willful act or omission in the care of such child was so gross, wanton, and culpable as to show a reckless disregard for human life is guilty of a . . . felony."

	subjects are likely to be incapable of making an informed decision regarding consent or are otherwise vulnerable to coercion or undue influence, such as . . . pregnant women . . . . whether additional safeguards have been included in the study to protect the rights and welfare of these subjects. . . ."			
Washington	None found	None found	WASH. REV. CODE ANN. § 9A.32.060 "(1) A person is guilty of manslaughter in the first degree when:. . .(b) He or she intentionally and unlawfully kills an unborn quick child by inflicting any injury upon the mother of such child."	WASH. REV. CODE § 9A.42.010 (4) "'Child' means a person under eighteen years of age." WASH. REV. CODE ANN. § 9A.42.020(1) "A parent of a child, the person entrusted with the physical custody of a child or dependent person is guilty of criminal mistreatment in the first degree if he or she, with criminal negligence, . . . causes great bodily harm to a child or dependent person . . . by withholding any of the basic necessities of life."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
				WASH. REV. CODE ANN. § 9A.42.030(1) "A parent of a child . . . is guilty of criminal mistreatment in the second degree if he or she with criminal negligence, . . . either (a) creates an imminent and substantial risk of death or great bodily harm by withholding any of the basic necessities of life, or (b) causes substantial bodily harm by withholding any of the basic necessities of life." *State v. Dunn*, 916 P.2d 952 (Wash. Ct. App., 1996) (citing WASH. REV. CODE ANN. § 9A.42.030(1)(a) and holding that where mother and newborn child tested positive for cocaine, "the State failed to establish that [the] unborn child was a "child" for the purposes of the criminal mistreatment statute" and that "the State failed to allege that [the mother] withheld a basic necessity of life").

WASH. REV. CODE ANN.
§ 9A.42.100

"A person is guilty of the crime of endangerment with a controlled substance if the person knowingly or intentionally permits a dependent child or dependent adult to be exposed to, ingest, inhale, or have contact with methamphetamine or ephedrine, pseudoephedrine, or anhydrous ammonia, including their salts, isomers, and salts of isomers, that are being used in the manufacture of methamphetamine, including its salts, isomers, and salts of isomers."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
West Virginia	None found	W. Va. Code Ann. § 61-2-30 "(c) . . . [A] pregnant woman and the embryo or fetus she is carrying in the womb constitute separate and distinct victims" of certain crimes of violence against the person including: first and second degree murder, voluntary manslaughter, attempt to kill or injure by poison, stalking and harassment, wanton endangerment involving the use of firearm, assault during commission of attempt to commit a felony, domestic violence, and DUIs. "(d) The provisions of this section do not apply to . . . "[a]cts or omissions of a pregnant woman with respect to the embryos or fetus she is carrying" nor to "acts or omissions by medical or health care personnel during or as a result of medical or health-related treatment or services. . . ."	W. Va. Code Ann § 61-2-30 "(a) This section may be known and cited as the Unborn Victims of Violence Act. (b) For the purposes of this article, the following definitions shall apply: *Provided,* That these definitions only apply for purposes of prosecution of unlawful acts under this section and may not otherwise be used: (i) To create or to imply that a civil cause of action exists; or (ii) for purposes of argument in a civil cause of action, unless there has been a criminal conviction under this section. (1) "Embryo" means the developing human in its early stages. The embryonic period commences at fertilization and continues to the end of the embryonic period and the beginning of the fetal period, which occurs eight weeks after fertilization or ten weeks after the onset of the last menstrual period. (2) "Fetus" means a developing human that has ended the embryonic period and thereafter continues to develop and mature until termination of the pregnancy or birth."	W. Va. Code Ann. § 49-1-201 "Abused child" includes "[a] child whose health or welfare is being harmed or threatened by: a parent, guardian, or custodian who knowingly or intentionally inflicts, attempts to inflict, or knowingly allows another person to inflict, physical injury or mental or emotional injury upon the child. . ." "Neglected child" includes "a child . . . [w]hose physical or mental health is harmed or threatened by a present refusal, failure or inability of the child's parent, guardian, or custodian to supply the child with necessary food, clothing, shelter, supervision, medical care, or education, when that refusal, failure, or inability is not due primarily to a lack of financial means on the part of the parent, guardian, or custodian; . . ."

"(c) . . . [A] pregnant woman and the embryo or fetus she is carrying in the womb constitute separate and distinct victims" of certain crimes of violence against the person including: first and second degree murder, voluntary manslaughter, attempt to kill or injure by poison, stalking and harassment, wanton endangerment involving the use of firearm, assault during commission of attempt to commit a felony, domestic violence, and DUIs.

"(d) The provisions of this section do not apply to.. "[a]cts or omissions of a pregnant woman with respect to the embryos or fetus she is carrying" nor to "acts or omissions by medical or health care personnel during or as a result of medical or health-related treatment or services. . . ."

In re A.L.C.M., 801 S.E.2d 260 (W.Va. 2017) (holding that "when a child is born alive, the presence of illegal drugs in a child's system at birth constitutes sufficient evidence that the child is an abused and/or neglected child, as those terms are defined by W. Va. Code § 49-4-601. [Footnote: "[W]e find our recent decision in *State v. Louk*, 237 W.Va. 200, 786 S.E.2d 219 (2016), to be distinguishable insofar as it decided matters regarding W. Va. Code § 61-8D-4a (1997) (Repl. Vol. 2014), a criminal statute, whereas the case *sub judice* arises in the context of abuse and neglect proceedings governed by W. Va. Code § 49-1-101 *et seq.*"]).

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Wisconsin	None found	None found	Wis. Stat. Ann. § 940.04 "(1) Any person, other than the mother, who intentionally destroys the life of an unborn child is guilty of a . . . felony . . . (2) Any person, other than the mother, who does either of the following is guilty of a . . . felony: (a) Intentionally destroys the life of an unborn quick child; or (b) Causes the death of the mother by an act done with intent to destroy the life of an unborn child. . . "(5) This section does not apply to therapeutic abortion which: (a) Is performed by a physician; and (b) Is necessary, or is advised by 2 other physicians as necessary, to save the life of the mother; and (c) Unless an emergency prevents, is performed in a licensed maternity hospital." "(6) In this section 'Unborn child' means a human being from the time of conception until it is born alive."	Wis. Stat. Ann. § 940.195 Wis. Stat. Ann. § 939.75 An individual that "causes substantial bodily harm to an unborn child by an act done with the intent to cause bodily harm to that unborn child, to the woman who is pregnant with that unborn child or another is guilty of a . . . felony." This provision does not apply to an "act that is committed in accordance with the usual and customary standards of medical practice during diagnostic testing or therapeutic treatment performed by, or under the supervision of a physician. . . ." It also does not apply to an "act by a woman who is pregnant with an unborn child that results in the death of or great bodily harm, substantial bodily harm, or bodily harm to that unborn child."

Wis. Stat. Ann. § 939.25

WI defines "criminal negligence" as including "ordinary negligence to a high degree, consisting of conduct that the actor should realize creates a substantial and unreasonable risk of death or great bodily harm to an unborn child, to the woman who is pregnant with that unborn child, or to another."

Wis. Stat. Ann. § 939.24

WI defines "criminal recklessness" as including conduct where an "actor creates an unreasonable and substantial risk of death or great bodily harm to an unborn child, to the woman who is pregnant with that unborn child or to another and the actor is aware of that risk."

continued

TABLE C-1 Continued

State	Fetal Research	Fetal Personhood	Fetal Homicide	Child Abuse/Neglect & Substance Abuse
Wyoming	None found	Wyo. Stat. Ann. § 6-1-104 (xviii) "Unborn child means a member of the species homo sapiens, at any state of development, who is carried in a womb."	Wyo. Stat. Ann. § 6-2-104 "A person is guilty of murder in the second degree of an unborn child if: (i) The person purposely and maliciously, but without premeditation, kills or attempts to kill any human being; (ii) The human being was pregnant with an unborn child; and (iii) The unborn child dies as a result of the person's actions."	Wyo. Stat. Ann. § 6-2-503 "A person is guilty of child abuse, a felony punishable by imprisonment for not more than ten (10) years" if that actor "intentionally or recklessly" inflicts physical injury, mental injury, or torture or cruel confinement upon a child under age 16 (if inflicted by a person who is not responsible for the child's welfare) or upon a child under age 18 (if inflicted by a person who is responsible for the child's welfare). Wyo. Stat. Ann. § 6-4-403 "No parent . . . shall knowingly or with criminal negligence cause, permit or contribute to the endangering of a child's life or health by violating a duty of care, protection or support."

"(b) No person shall knowingly . . . sell, give or otherwise furnish a child any drug prohibited by law without a physician's prescription."

"'Child' means any person under the age of sixteen (16) years."

continued

D

Assessing U.S. Food and Drug Administration Authorities, Guidance, and Policies for Prescription Drug, Biological Product, and Medical Device Development and Commercialization for Use by Pregnant and Lactating Women

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INTRODUCTION

While many pregnant and lactating women may require at least one medication or device intervention during these phases of life, there is often little information available about the appropriate use and overall safety of these interventions in pregnant and lactating women. In particular, the U.S. Food and Drug Administration (FDA) has acknowledged that development of therapeutics for use in pregnant and lactating women has trailed behind the development of therapeutics for other populations. In this paper, we have summarized FDA authorities, guidance, and policies relating to drug, biological product, and medical device development and commercialization that are specific to pregnant and lactating women. We provide an overview of how FDA reviews and authorizes testing and marketing of prescription drugs, biological products, and medical devices, with a specific focus on requirements that are specific to obtaining safety and efficacy information for use of such interventions in pregnant and lactating women.

METHODS

Throughout this paper, we use a number of defined terms. We have focused our review of FDA's authorities, guidance, and policies on prescription products. When we refer to "prescription products," we are including (1) drugs approved by FDA pursuant to a New Drug Application (NDA); (2) biological products approved by FDA pursuant to a Biologics License Application (BLA); and (3) medical devices that have come to market through FDA's premarket approval, de novo authorization, or premarket notification pathways. For medical devices subject to these pathways for market entry, we collectively use the term *approval* when referring to the regulatory process for obtaining market entry. This paper does not summarize FDA authorities, guidance, or policy relating to over-the-counter drugs or devices. When we refer to a product as *investigational*, we mean a drug, biological product, and/or medical device that is not yet authorized by FDA for marketing or commercial distribution in the United States and is subject to the requirements of FDA's Investigational New Drug (IND) Application, in the case of drugs and biologics, or investigational device exemption (IDE), in the case of medical devices. When an FDA authority, guidance, or policy is specific to a particular product type (i.e., drugs, biological products, and/or medical devices), such term(s) are used in a distinct manner to signify the specific requirements for the particular product type.

We reviewed FDA's authorities, guidance (with a primary focus on those currently in effect, whether draft or final), and policies requiring or recommending that sponsors obtain information to inform the safe and effective use of prescription products (irrespective of the indication(s) for use) by pregnant and lactating women, as well as those authorities that authorize FDA to require or mandate labeling changes for approved interventions when new information becomes available. Where applicable, we reviewed the *Federal Register* docket for draft FDA regulations and guidance, including public comments submitted to the applicable FDA dockets. We also reviewed FDA's responses relating to potential incentives or disincentives for sponsors to obtaining information to inform the safe and effective use of prescription products for use by pregnant and lactating women. Our review of public comments and FDA's responses focused in particular on health care professionals, medical societies and associations, industry members and industry associations.

We also reviewed other FDA public resources, such as FDA workshop and public meeting transcripts, action plans, and FDA reports related to the inclusion of pregnant and lactating women in clinical research to support prescription product use in these populations. We also researched relevant FDA statistics, as well as FDA's databases, relating to approved or currently marketed prescription products with respect to their labeling content, postmarketing commitments (PMCs) and postmarketing

requirements (PMRs), and supportive clinical data in pregnant and lactating women. We also searched ClinicalTrials.gov for a sampling of industry-sponsored clinical trials involving investigational products that are or were conducted in the United States and that proactively enrolled pregnant and/or lactating women.

RESULTS

The mission of FDA is to protect the U.S. public health by ensuring the safety and efficacy of prescription products prior to public availability. Drugs and medical devices are subject to regulation under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and biological products are subject to regulation under the FD&C Act and the Public Health Service Act (the PHS Act), as well as other federal, state, and local statutes and regulations. Both the FD&C Act and the PHS Act and their implementing regulations (as applicable) govern, among other things, the preclinical testing, clinical trials, labeling, safety and efficacy, packaging, manufacturing, distribution, advertising and promotion, and post-approval studies and surveillance of drugs, biological products, and medical devices. For purposes of this summary, we focused on preclinical testing, clinical trials, approval, labeling, and postapproval studies and surveillance requirements enumerated in statutes and regulations, as well as recommendations described in FDA guidance documents or FDA policies (neither of which establish legally enforceable responsibilities). We identified numerous relevant FDA authorities related to drugs and biological products but not medical devices. Given that medical devices are generally used for procedures and have a specific intended use based on their FDA classification, this was not unexpected and, as such, our findings primarily relate to requirements and recommendations for sponsors of drugs and biological products.

Our review concluded that FDA has demonstrated a commitment to protecting and advancing the public health of pregnant and lactating women in the following ways: (1) requiring certain preclinical testing to uncover potential developmental and/or fetal toxicities; (2) recommending the inclusion of pregnant women in clinical trials; and (3) requiring the presentation of pregnancy and lactation risk information and clinical considerations in drug and biological product labeling to support informed prescribing decisions in these populations. However, we also observed that FDA maintains no single database of prescription drugs, biological products, or medical devices that are indicated for use by pregnant and lactating women. While sponsors are required to list and post results for certain clinical trials evaluating drugs, biological products, and medical devices on ClinicalTrials.gov, our search of the platform did not easily identify interventional clinical trials that enrolled or are currently enrolling pregnant and lactating women.

We also observed that as of 2021, FDA has only approved nine drugs specifically for nononcology obstetrical indications, and to date there have been numerous devices authorized for obstetrical and gynecological use. It is unclear whether FDA has approved any prescription products specifically for a stipulated use in lactating women, and the authorized prescription devices for the lactating population appear to be limited to breast pumps. As of December 2018, FDA has withdrawn three prescription products from the market that were related to pregnancy and lactation: (1) diethylstilbestrol; (2) bromocriptine mesylate; and (3) Makena (hydroxyprogesterone caproate). There are also 13 prescription products that are subject to a risk evaluation and mitigation strategy (REMS) program to minimize embryo-fetal toxicities in pregnant or lactating patients. Additionally, of the approximately 2,300 PMRs and PMCs listed in FDA's database, around 2.6 percent involved preclinical developmental and reproductive toxicity (DART) studies, around 0.2 percent involved clinical trials in pregnant individuals, around 1.2 percent involved clinical lactation studies, and approximately 8 percent involved a pregnancy registry or other prospective and/or retrospective observational study in pregnant and lactating individuals. Based on our review of FDA's authorities, guidance, and policies on prescription products that specifically relate to pregnancy and lactation, we provide a list of discrete considerations and opportunities that may support regulatory initiatives relating to the development and commercialization of prescription products for use by pregnant and lactating women.

Preclinical Testing

Overview

Before testing any prescription drug or biological product in humans, FDA requires that the product undergo preclinical (also referred to as *nonclinical*) testing, which includes laboratory evaluations of the product's characteristics, chemistry, toxicity, and formulation, as well as animal studies to assess the potential safety and activity of the product to support use of the product in clinical trials. The results of these preclinical studies aid in determining an initial starting dose, dose titration, and the highest safe dose for human clinical trials, while also initially characterizing potential adverse effects that might occur in humans (ICH, 2020).

As a part of an IND application to initiate a clinical trial for an investigational drug and biological product, FDA requires inclusion of:

> [a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of

> animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. . . As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety (21 CFR § 312.23(a)(8)).

Developmental and Reproductive Toxicity (DART) Studies

Generally, when adult men and women are to be enrolled in clinical trials, preclinical DART studies are conducted to reveal any effect of the drug or biological product on mammalian reproduction that may be relevant for human risk assessment. FDA's guidance documents relating to preclinical DART studies primarily include ICH S5(R3) "Detection of Reproductive and Human Developmental Toxicity for Human Pharmaceuticals" and ICH M3(R2) "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," which have been adopted by FDA and were issued to industry as final guidance in 2021 and 2010, respectively (ICH, 2020; ICH, 2009a). However, ICH S5(R3) states "No guidance can provide sufficient information to cover all possible cases, and flexibility in testing strategy is warranted" (ICH, 2020).

The following six stages of reproduction are generally assessed in DART studies:

Stage 1: premating to conception
Stage 2: conception to implantation
Stage 3: implantation to closure of the hard palate
Stage 4: closure of the hard palate to the end of pregnancy
Stage 5: birth to weaning
Stage 6: weaning to sexual maturity (ICH, 2020)

The above stages have typically been evaluated using three in vivo study types:

- fertility and early embryonic development (FEED) studies, which assess stages 1 and 2;
- embryo–fetal development (EFD) studies in two species, which assess stages 3 and 4; and
- pre- and postnatal development (PPND) studies, which assess stages 3 through 6 (ICH, 2020).

FEED studies aim to test for adverse effects of new drugs and biologics on both male and female fertility, as well as implantation and

development of the embryo. These studies are typically conducted in rodents, with treatment of the investigational product beginning before mating and continuing until after implantation of the embryo. EFD studies aim to detect adverse effects on the pregnant animal and survival and the development of the embryo and fetus following treatment of the investigational product upon embryo implantation until just prior to birth. These studies are typically conducted in both rodent and nonrodent species. PPND studies aim to detect adverse effects following exposure of the pregnant animal from implantation of the embryo through weaning in order to evaluate effects on the pregnant or lactating female and development of the offspring (ICH, 2020).

According to ICH, the risks to all stages (considered one complete life cycle—from conception in one generation through conception in the following generation) should be assessed unless the stage is not relevant to the intended population. The stages assessed in individual studies are at the discretion of the sponsor, but the timing of studies within the product development process is dependent on the intended study populations and phase of development. According to ICH, there are several key factors sponsors should consider when developing an overall integrated testing strategy to evaluate effects on reproduction and development. ICH notes sponsors should consider the target patient population and therapeutic indication for their investigational product, which may influence whether DART studies evaluating all stages of reproduction and development are warranted (see "Preventive and Therapeutic Vaccines for Infectious Diseases and Oncology Products" section below). Additionally, ICH further notes the timing for conducting specific DART assessments "should take into consideration the need for these data to support the safe use of the pharmaceutical in clinical trials or the intended patient population" (ICH, 2020).

The ICH M3(R2) "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" further elaborates on the timing and conduct of DART studies based on the target patient population for a planned or proposed clinical trial, noting the following:

- Men can be included in Phase I and Phase II clinical trials before the conduct of a preclinical male fertility study since an evaluation of the male reproductive organs is performed as part of another preclinical toxicity study, called the repeated-dose toxicity study, which is required to initiate clinical trials of an investigational drug or biological product in humans. A preclinical male fertility study should be completed before initiation of large-scale or long-duration clinical trials (ICH, 2009a).
- Women not of childbearing potential can be included in clinical trials without DART studies if the relevant preclinical repeated-dose toxicity

studies, which include an evaluation of the female reproductive organs, have been conducted (ICH, 2009a).

- For women of childbearing potential (WOCBP), it is important to characterize and minimize the risk of unintentional exposure of the embryo or fetus, which can be achieved by conducting DART studies to characterize the risk of the drug and take appropriate precautions during exposure of WOCBP in clinical trials, or limit the risk by taking precautions to prevent pregnancy during clinical trials (ICH, 2009a).
  - In all ICH regions, including the United States, the European Union (EU), and Japan, WOCBP can be included in early clinical trials without DART studies in certain circumstances. Two examples of such circumstances provided in the guidance include intensive control of pregnancy risk over short duration (e.g., 2 weeks) clinical trials, and where there is a predominance of the disease in women and the objectives of the trial cannot be effectively met without the inclusion of WOCBP and there are sufficient precautions to prevent pregnancy during the trial (ICH, 2009a). Where appropriate preliminary DART data are available from two species and where precautions to prevent pregnancy in clinical trials are used:

    > inclusion of WOCBP (up to 150) receiving investigational treatment for a relatively short duration (up to 3 months) can occur before conduct of definitive reproduction toxicity testing. This is based on the very low rate of pregnancy in controlled clinical trials of this size and duration, and the ability of adequately designed preliminary studies to detect most developmental toxicity findings that could raise concern for enrollment of WOCBP in clinical trials. The number of WOCBP and the duration of the study can be influenced by characteristics of the population that alter pregnancy rates (e.g., age, disease) (ICH, 2009a).

  - In the United States EFD studies can be deferred until the initiation of Phase III trials, the final phase of clinical research prior to submitting marketing applications, for WOCBP where there are precautions to prevent pregnancy in the trial. In the EU and Japan, for example, other than in the circumstances described above, definitive DART studies should be completed before exposure of WOCBP. In all ICH regions, WOCBP can be included in repeated-dose Phase I and Phase II trials before the conduct of a preclinical female fertility study where a preclinical repeated-dose toxicity study is performed. Nonclinical studies that specifically address female fertility should be completed to support inclusion of WOCBP in large-scale or long-duration clinical trials (ICH, 2009a).

    - In all ICH regions, including the United States, the PPND study should be submitted for marketing approval (ICH, 2009a).
    - Lastly, all preclinical female reproduction toxicity studies and standard genotoxicity tests should be completed before the inclusion of WOCBP not using highly effective birth control in any clinical trial (ICH, 2009a).
- Pregnant women should only be included in clinical trials after all preclinical female reproduction toxicity studies and standard genotoxicity studies have been conducted. Additionally, any safety data from previous human exposure should be evaluated prior to inclusion (ICH, 2009a).

In June 2023, FDA issued a final guidance entitled, "Nonclinical Evaluation of Immunotoxic Potential of Pharmaceuticals," which is intended to assist sponsors in the nonclinical evaluation of the immunotoxic potential of drugs and biological products and provides expanded guidance to sponsors for approaches for assessing the effects of immunotoxicants on pregnancy and developmental immunotoxicity. The final guidance states that for pharmaceuticals that are not intended to affect the immune system, the risk for adverse effects on the maternal immune system that can affect implantation and gestation would typically be identified in nonclinical FEED and EFD studies and such studies would be considered adequate for assessing such risk. For pharmaceuticals that are intended to affect the immune system, FEED and EFD studies may be useful in characterizing similar risks; however, if the mechanism of action of the pharmaceutical is known to be incompatible with fertility or maintenance of pregnancy, it may be appropriate to assess the risk to implantation and pregnancy based on a weight-of-evidence approach. The final guidance also notes that FEED and EFD studies are not generally warranted for pharmaceuticals intended to treat patients with advanced cancer (FDA, 2023a).

Product-Specific Guidance—Preventive and Therapeutic Vaccines for Infectious Diseases

In February 2006, FDA published a final guidance, "Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications," which sets forth recommendations for the assessment of developmental toxicity of preventive and therapeutic vaccines for infectious disease indicated for females of childbearing potential and pregnant individuals. In this guidance, FDA states the target population for vaccines often includes females of childbearing potential who may become pregnant during the vaccination period, and "Unless the vaccine is specifically indicated for maternal immunization, no studies are

conducted prior to product licensure to determine the vaccine's safety in pregnant women" (FDA, 2006a). FDA goes on to further state:

> Because pregnant women are usually excluded from clinical trials, data from developmental toxicity studies in animal models offer one approach to screen for potential developmental hazards. Studies in animal models may frequently present the only information available to draw conclusions regarding developmental risk to be included in the product labeling required under section 201.57(f)(6) in Title 21 Code of Federal Regulations (§ 201.57(f)(6)) (FDA, 2006a).

FDA recommends sponsors consider conducting preclinical developmental toxicity studies for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women, as well as for vaccines indicated for adolescents and adults (FDA, 2006a). The final guidance describes the recommended timing for conducting preclinical developmental toxicity studies to support the inclusion of either pregnant individuals or WOCBP in clinical trials based on the vaccine's intended indicated population as follows:

- Maternal immunization: For vaccines indicated specifically for immunization of pregnant women, sponsors should have nonclinical developmental toxicity study data available prior to the initiation of any clinical trial enrolling pregnant women (FDA, 2006a).
- WOCBP: For vaccines indicated for WOCBP, sponsors may include such subjects in clinical trials without having conducted nonclinical developmental toxicity studies prior to initiation, provided that appropriate precautions are taken by subjects enrolled in these trials to avoid vaccination during pregnancy (e.g., pregnancy testing, birth control). Developmental toxicity study data should be included with the BLA for the product regardless of whether such information was previously submitted with the IND (FDA, 2006a).
- Males: Males may be included in clinical trials in the absence of nonclinical male fertility studies, but such studies may be recommended for certain products in the future (FDA, 2006a).

FDA notes "The decision whether a developmental toxicity study needs to be performed should be made on a case-by-case basis taking into consideration historical use, product features, intended target population, and intended use" (FDA, 2006a).

Product-Specific Guidance—Oncology Products

In October 2019, FDA issued a final guidance, "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations,"

which describes less stringent preclinical DART study considerations for most anticancer agents than for other diseases. Specifically, the final guidance states that while an EFD toxicity assessment is needed to support marketing applications for the treatment of patients with advanced malignancies, fertility and PPND studies are generally not warranted, but for pharmaceuticals used in certain adjuvant or neoadjuvant indications, fertility and PPND studies may be needed on a case-by-case basis and results could be submitted after approval (FDA, 2019a). ICH S9 "Nonclinical Evaluation for Anticancer Pharmaceuticals," which was adopted by FDA as final guidance in 2010), expands on this principle and states that a fertility and early embryonic development study is not warranted to support clinical trials or a marketing application of pharmaceuticals intended for the treatment of patients with advanced cancer (ICH, 2009b).

Clinical Trials

Overview

FDA-regulated clinical trials involve the administration of an investigational prescription drug, biological product, or medical device to human subjects under an FDA-authorized IND for investigational drugs and biological products or an IDE application for medical devices and are conducted to assess the safety and efficacy of the new therapeutic or device for the treatment, prevention, or mitigation of a particular disease (21 CFR § 312.20; 21 CFR § 812.20). Such clinical trials must be conducted in accordance with good clinical practice requirements, which include the requirement that all trial subjects provide their informed consent in writing for their participation in any clinical trial as well as obtaining and maintaining institutional review board (IRB) approval for the clinical trial until completion (21 CFR Part 50; 21 CFR Part 56).

In the last 2 decades, FDA has issued a number of guidance documents related to the inclusion of pregnant and lactating women in clinical trials. FDA has been active in this area, repeatedly updating and refining its guidance for industry and approach since its initial 1977 guidance advising that nonpregnant WOCBP should be excluded from Phase I and early Phase II studies (FDA, 1977). This 1977 guidance was lifted in 1993 with the implementation of FDA's final guidance, "Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," which recommended that analyses be performed to assess differences in drug action attributable to gender in controlled clinical trials and emphasized that, where appropriate, WOCBP should use contraception or abstinence while participating in early clinical trials (FDA, 1993).

Shortly thereafter, in 2000, FDA issued a final rule amending its "Clinical Hold Regulations for Products Intended for Life-Threatening Disease" promulgated at 21 CFR § 312.42 to allow FDA to place a clinical hold on clinical trials for the treatment of a serious or life-threatening disease if "women with reproductive potential" (or men) with the disease or condition being studied were excluded from a clinical trial solely because of risk or potential risk of reproductive or developmental toxicity from use of the investigational drug or biological product (FDA, 2000a). One comment to the proposed rule was received stating that "pregnant women have the same right to make informed decisions about their own treatment as other women with reproductive potential" and concluded by recommending that the proposed regulation also apply if pregnant women are excluded from clinical trials for life-threatening diseases. FDA responded that it did not intend the phrase "women with reproductive potential" to include pregnant women (and this clarity was added to the regulations), and that it did not question pregnant women's ability to provide informed consent. However, FDA noted there is "increased complexity in conducting clinical trials with pregnant women because of their changing physiology. FDA will continue to explore this issue in other forums" (FDA, 2000b).

Inclusion of Pregnant Women in Clinical Trials

FDA-regulated clinical trials that include pregnant women must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR Part 50 [informed consent]; 21 CFR Part 56 [IRBs]). In addition, if the trial is supported or conducted by the U.S. Department of Health and Human Services (HHS), then the federal regulations found in 45 CFR Part 46 may also apply, which would include compliance with subpart B, "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research." FDA regulations do not contain a section similar to 45 CFR Part 46, subpart B; however, FDA recommends that these requirements be satisfied and has referred to the requirements of subpart B in certain of its own guidance documents for FDA-regulated clinical trials (outlined below) (FDA, 2018a).

Where appropriate, such as when sponsors may enroll WOCBP in clinical trials evaluating their investigational products, FDA requires a statement in the informed consent form that the investigational product or procedure may involve risks to the study subject, or to the embryo or fetus, which are currently unforeseeable (21 CFR § 50.25(b)(1)). Under FDA's final guidance issued in August 2023, "Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors," FDA explains that if long-term preclinical safety studies are not completed, the informed consent process should explain that researchers have not completed such studies

that may identify potential unforeseeable risks (e.g., carcinogenicity or teratogenicity studies), including risks to the embryo or fetus if the study subject is or becomes pregnant (FDA, 2023b).

For sponsors planning on including pregnant women in clinical trials of their investigational prescription drug, biological product, or medical device, FDA recommends that sponsors be prepared to discuss such plans with the appropriate FDA review division early in the development phase, and such discussions should involve FDA experts in bioethics and maternal health (FDA, 2018a, 2013a).

FDA's 2004 final guidance, "Pharmacokinetics in Pregnancy, Study Design, Data Analysis, and Impact on Dosing and Labeling," provides specific recommendations for designing and conducting pharmacokinetic studies (PK) and pharmacodynamic (PD) studies in pregnant women and lays out a framework to stimulate further study and research to assist in rational therapeutics for pregnant patients. Acknowledging that (1) pregnant women are "actively excluded" from clinical trials, (2) data in product labels regarding PK and dose adjustments during pregnancy rarely provide information for appropriate prescribing in pregnancy, and (3) there has been a significant amount of pharmacological research conducted to improve the quality and quantity of data available for other altered physiologic states (e.g., patients with renal and hepatic disease) and subpopulations (e.g., pediatric patients), FDA states "The need for PK/PD studies in pregnancy is no less than for these populations, nor is the need for the development of therapeutic treatments for pregnant women" (FDA, 2004). This guidance specifies that pregnant women may be involved in PK studies if the following conditions are met (45 CFR subpart B, § 46.204):

1. Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and
2. The risk to the fetus is not greater than minimal, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means (FDA, 2004).

Additionally, FDA's final guidance recommends that PK studies be conducted in pregnant women in any of the following situations:

1. The drug is known to be prescribed in or used by pregnant women (especially in the second and third trimesters) (FDA, 2004).
2. It is a new drug or indication, if there is anticipated or actual use of the drug in pregnancy (FDA, 2004).

3. Use is expected to be rare, but the consequences of uninformed dosages are great (e.g., narrow therapeutic range drugs, cancer chemotherapy) (FDA, 2004).
4. Pregnancy is likely to alter significantly the PK of a drug (e.g., renally excreted drug) and any of the above apply (FDA, 2004).

FDA guidance provides that PK studies in pregnant women are not recommended if the drug is not used in pregnant women or the drug has known or highly suspect fetal risk. FDA further states in this guidance:

> Although PK studies in pregnancy can be considered in Phase III development programs depending on anticipated use in pregnancy and the results of reproductive toxicity studies, FDA anticipates that most PK studies in pregnant women will occur in the postmarketing period and will be conducted using pregnant women who have already been prescribed the drug as therapy by their own physician (FDA, 2004).

FDA's draft guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials," provides the most expansive current guidance to industry on how and when to include pregnant women in clinical trials for drugs and biological products. This guidance discusses both the scientific and ethical issues that sponsors should address when considering the inclusion of pregnant women in clinical trials (FDA, 2018a).

FDA recommends sponsors consider including an ethicist in planning their drug development programs because of the complex ethical issues involved when including pregnant women in their clinical trials. If an IRB regularly reviews research involving pregnant women, the IRB must consider including one or more individuals who are knowledgeable about and experienced in working with such subjects (21 CFR § 56.107(a)), and IRBs are required to determine that additional safeguards are included in the trial to protect the rights and welfare of subjects who are pregnant (21 CFR § 56.111(b)) (FDA, 2018a). FDA does not appear to have expanded on, either through regulation or guidance, what these "additional safeguards" may be in the context of research involving pregnant women.

This 2018 guidance provides that pregnant women may be enrolled in clinical trials that involve greater than minimal risk to the fetuses. When a trial offers the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses, it can be acceptable to expose a fetus to greater than minimal risk. FDA provides examples of when such exposure would be acceptable, which include when a trial offers a needed but otherwise unavailable therapy or when a drug or biological product being studied reduces the risk of acquiring a serious health condition (FDA, 2018a).

Importantly, FDA explicitly states in this 2018 guidance that FDA considers it ethically justifiable to include pregnant women with a disease

or medical condition requiring treatment in clinical trials under the following circumstances:

- For FDA-approved drugs being studied in the postmarketing setting, it is justifiable to include pregnant women with the disease or medical condition when: (1) adequate nonclinical studies (including DART studies) have been completed; (2) there is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women; and (3) either efficacy cannot be extrapolated and/or safety cannot be assessed by other study methods (FDA, 2018a).
- For investigational drugs and biological products (regardless of the indication), it is justifiable to include pregnant women with the disease or medical condition when: (1) there have been adequate nonclinical studies completed; and (2) the clinical trial holds out the prospect of direct benefit to the pregnant woman and/or the fetus that is not otherwise available outside of the research setting or cannot be obtained by any other means (FDA, 2018a).
- For a woman who becomes pregnant while already enrolled in a clinical trial, her continued inclusion and treatment with the investigational therapy is justified when the risks and benefits have been evaluated post unblinding and counseling and the pregnant participant completes a second informed consent process that includes the additional risk–benefit considerations given the pregnancy. If a woman becomes pregnant while enrolled in a clinical trial and fetal exposure to the investigational therapy has already occurred, the woman should be allowed to continue on the investigational therapy if the potential benefits of continued treatment for the woman outweigh the risks of ongoing fetal exposure to the investigational therapy, the risks of discontinuing maternal therapy, and/or the risks of exposing the fetus to additional drugs if placed on an alternative therapy. Regardless of whether the woman continues in the trial, FDA states that it is important to collect and report the pregnancy outcome (FDA, 2018a).

According to FDA's draft guidance for drug developers, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," pre-IND and later clinical-stage meetings between FDA and sponsors can include discussion of trial populations as well as design plans (FDA, 2017). Additionally, for developers of medical device products, FDA's final guidance, "Requests for Feedback and Meetings for Medical

Device Submissions: The Q-Submission Program," provides a similar opportunity for interaction between sponsors and FDA on matters involving study design and population plans (FDA, 2023c). However, FDA notes in its medical device draft guidance:

> Resource constraints do not permit FDA to prepare or design particular study plans. If a submitter would like FDA's feedback on a protocol, they should submit a proposed outline, with a rationale for the chosen approach.
>
> For more productive feedback, we recommend that the submitter include specific questions about their protocol. Without directed questions, FDA's feedback may be more general in nature and not provide adequate specifics on the area of interest (FDA, 2023c).

As such, in both cases, the nature of information exchange from FDA to the sponsor is generally framed for sponsors as reactive feedback on what a sponsor submits to or asks of FDA rather than a proactive inquisition by FDA of the sponsor to help proactively recommend to sponsors the best design for a particular clinical trial program. As a result, the possibility for a proactive recommendation by FDA to include pregnant women in clinical trials may be limited to occasions where a sponsor has directly placed a question or trial design before FDA that outlines plans to include pregnant women in a clinical trial. However, other than FDA's resource constraints, we are not aware of any reason FDA would be prohibited under its current authorities from proactively discussing the inclusion of pregnant women in clinical trial programs that sponsors submit for FDA review and feedback.

When pregnant women are enrolled in a clinical trial, FDA's draft guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials," provides that data collection elements should include (at a minimum): (1) gestational age at enrollment; (2) gestational timing and duration of drug exposure; and (3) pregnancy outcomes including adverse maternal, fetal and neonatal events. Further, the draft guidance states while all clinical trials require monitoring, clinical trials that involve pregnant women should include a data monitoring plan that includes members with relative specialty and perinatal expertise to permit ongoing recognition and evaluation of safety concerns that arise during the course of the trial (FDA, 2018a).

The draft guidance also states that there may be situations where it would be appropriate to stop a randomized, controlled clinical trial that is enrolling pregnant women, such as when an appropriately planned interim analysis demonstrates superior efficacy of the control or active comparator arm, or when there are documented serious maternal or fetal adverse events that can be reasonably attributed to drug exposure and are

deemed to exceed the potential benefits of drug treatment (FDA, 2018a). We did not identify any analyses or other reports, either by FDA or third parties, evaluating the effect of FDA's 2018 guidance on industry's inclusion of pregnant women in clinical trials.

In 2019, FDA updated its draft guidance, "Clinical Lactation Studies: Considerations for Study Design," which provides recommendations for sponsors conducting pre- or postmarketing clinical lactation studies. The draft guidance clarifies that while FDA has required lactation studies under section 505(o)(3) of the FD&C Act under certain circumstances to inform breastfeeding with drug use recommendations included in the "Lactation" subsection of labeling, the draft guidance states that FDA "is considering additional circumstances in which lactation studies may be required" (FDA, 2019b).

FDA's clinical lactation studies guidance encourages sponsors to consider conducting clinical lactation studies even when not required, such as when a drug under review for approval is expected to be used by women of reproductive age, use of a drug in lactating women becomes evident after approval, the sponsor is seeking a new indication for an approved drug that provides evidence of use or anticipated use of the drug by lactating women, and when marketed medications are commonly used by women of reproductive age (FDA, 2019b).

Inclusion of Lactating Women in Clinical Trials

Similar to clinical trials involving pregnant women, FDA-regulated clinical trials involving lactating women must conform to all applicable FDA regulations. However, FDA has recommended, through its draft guidance on clinical lactation studies, that sponsors should consider the following additional ethical considerations for clinical lactation studies:

- In the postapproval setting, it is ethically acceptable to enroll a woman in a clinical trial of an approved drug where the woman has already made a decision to take the drug (as a part of her standard of care) while breastfeeding and allow the woman to continue breastfeeding while taking the drug in the clinical trial (FDA, 2019b).
- In the research setting, FDA's draft guidance states:

  > Where a woman who is currently breastfeeding starts an investigational drug [or biological product] for a disorder or condition, breastfeeding must be discontinued for the duration of the study because the risks of the exposure to the drug [or biological product] in the breastfeeding infant may outweigh the benefits. The potential drug exposure of a breastfeeding infant must be considered a research risk (and offers no clinical benefit to the infant) (FDA, 2019b).

However, it is acceptable to enroll breastfeeding women who are participating in a clinical trial of an investigational drug or biological product in clinical lactation studies if the breastfeeding woman agrees to temporarily pump and discard milk to avoid exposing the infant to the investigational product. The length of time that the milk will need to be discarded should be specified in the clinical trial protocol and will vary depending on factors such as the half-life of the investigational product (FDA, 2019b).

- In a research setting "where a healthy woman who is currently breastfeeding volunteers for a clinical lactation study, breastfeeding must be discontinued for the duration of the study so that an infant is not exposed to the investigational drug [or biological product]" (FDA, 2019b).

As noted above with respect to the inclusion of pregnant women in clinical trials, the same FDA guidances on formal meetings between the sponsors and FDA are relevant in providing an opportunity for FDA feedback on the inclusion of lactating women in clinical trials of prescription products. As noted above, because formal meetings are generally structured for FDA to provide reactive feedback in response to information and questions that a sponsor submits, the possibility for FDA feedback on the inclusion of lactating women in clinical trials may be limited to instances where a sponsor has directly sought such feedback in the questions it has submitted to FDA or where feedback is sought from FDA on the study population that includes lactating women. Again, other than FDA's resource constraints, we are not aware of any reason FDA would be prohibited under its current authorities from proactively discussing the inclusion of lactating women in clinical trial programs that sponsors submit for FDA review and feedback.

Recent Efforts Relating to Increasing Diversity in Clinical Trials

FDA's most recent efforts in this space relate to increasing diversity in clinical trials. In 2020, FDA issued a final guidance, "Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs," which provides recommended approaches that sponsors of clinical trials intended to support an NDA or a BLA can take to increase enrollment of underrepresented populations in clinical trials. This guidance encourages sponsors to consider various trial designs and methodologies to help facilitate the enrollment of a broader population in the clinical trial, but FDA recognizes that certain exclusions are appropriate when necessary to help protect individuals, such as pregnant and lactating women who are "frequently excluded from clinical trials when there is inadequate information to assess the risk to the fetus or

infant" (FDA, 2020a). The final guidance includes several recommendations for increasing diversity in clinical trials, but the only recommendation relating to the inclusion of pregnant and lactating women is for sponsors to consider including PK sampling to establish dosing for women who become pregnant during a trial "when it is possible for continued participation with sufficient assurances of safety, and if the risks to the participant and fetus of continued trial participation are reasonable in relation to the anticipated benefits and the importance of the knowledge that may be expected to result." Over time, this may provide important information on drug metabolism during pregnancy and across trimesters (FDA, 2020a).

In 2022, FDA published its draft guidance, "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials," which builds on its 2020 final guidance and advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, and to include pregnancy and lactation status as underrepresented populations. This guidance further states "Some individuals from these groups have often been underrepresented in medical product development, and FDA considers their representation in clinical trials and studies to be a priority," (referring to enrollment of women, and pregnant or lactating women) (FDA, 2022a). FDA encourages sponsors to submit race and ethnicity diversity plans for their clinical trials that ensure adequate participation of these underrepresented populations to provide important information pertaining to medical product safety and effectiveness for product labeling (FDA, 2022a).

Under the Food and Drug Omnibus Reform Act of 2022 (FDORA), sponsors of prescription investigational drugs, biological products, and medical devices will be required, unless waived by FDA, to submit a diversity action plan for all Phase III clinical trials, or as appropriate, another pivotal study conducted under an IND or IDE, in support of a marketing application. Under FDORA, these plans must be submitted no later than when sponsors submit their Phase III or other pivotal trial protocol, and FDA has the authority to modify the plan or waive the requirement for the plan in certain circumstances (such as if conducting the trial in accordance with a diversity action plan would otherwise be impracticable). FDORA requires FDA to issue new draft guidance or update existing draft guidance within 12 months of enactment of FDORA (FDORA, 2022).

Building on FDA's 2022 draft diversity guidance, FDA published a draft guidance in August 2023 titled, "Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products." The draft guidance reemphasizes the

importance of including patient populations in clinical trials that are historically underrepresented in clinical research (e.g., populations based on race, ethnicity, sex, and age), and FDA notes that efforts should be made, both in the pre- and postmarket settings, to include other underrepresented populations, including those based on pregnancy status and lactation status (FDA, 2023d).

Congress, through Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), created ClinicalTrials.gov to "increase the availability of information to the public" and to "communicate the risks and benefits of drugs [and devices]" in order to "help patients, providers, and investigators learn new information and make more informed health care decisions" (FDAAA, 2007). Using ClinicalTrials.gov, we attempted to evaluate current uptake by industry of FDA's recommendations and the effect of required diversity action plans by researching the number of clinical trials that have enrolled or are currently enrolling adult pregnant and lactating women. Our research results on ClinicalTrials.gov identified 719 clinical trials that were initiated between January 1, 2022, and August 1, 2023, that were interventional (i.e., involved a drug, biological product, or device), funded by industry (as opposed to a U.S. federal agency, individual, or university), enrolled or were enrolling adult female participants (including healthy volunteers), and were early Phase I, II, III, or IV trials that had trial sites in the United States. Owing to the limitations of the search functionality, any search of *pregnant* or *lactating* (or variations of these terms) under the eligibility criteria section of ClinicalTrials.gov identified clinical trials where *pregnant* or *lactating* (or variations of these terms) were listed as *either* an inclusion *or* exclusion criteria. Additionally, owing to the variability of terms used by sponsors in describing the eligibility criteria for their clinical trials (as there are no enforced formatting rules or guidelines), the search results on ClinicalTrials.gov could not be refined to those clinical trials that affirmatively enrolled or were enrolling pregnant and lactating women. As a result, there is currently no effective research tool or database we are aware of to measure the effect of FDA's recommendations and required diversity action plans on increasing research enrollment opportunities for pregnant and lactating women.

Review and Approval

Overview

Following completion of the necessary preclinical tests and clinical trials, the results of the preclinical tests and clinical trials, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things, are submitted to

FDA as part of an NDA, in the case of drugs, and a BLA, in the case of biological products, requesting approval to market the product for one or more indications.

In September 2011, FDA issued a final guidance titled, "Reproductive and Developmental Toxicities—Integrating Study Results to Assess Concerns," which is intended to describe an approach for applicants of NDAs and BLAs to estimating possible human developmental or reproductive risks associated with drug or biological product exposure when a nonclinical finding of toxicity has been identified but definitive human data are unavailable to help ensure a consistent review by FDA review staff. FDA notes that the approach presented in the final guidance is used when there is a toxicity finding and involves the integration and consideration of a variety of nonclinical information, including reproductive toxicology, general toxicology, and toxicokinetic and PK information; however, "Available clinical information to evaluate a drug's potential to increase the risk of an adverse developmental or reproductive outcome in humans should be evaluated separately and, when definitive, can supersede any nonclinical findings" (FDA, 2011a).

The final guidance defines two broad toxicity categories—reproductive (i.e., structural and functional alterations that affect reproductive competence in sexually mature male and females) and developmental (i.e., adverse effects on the developing organism that result from exposure prior to conception, during the prenatal period, or postnatally up to the time of sexual maturity)—and further categorizes eight classes of possible effects that may be considered during the nonclinical data integration and assessment:

- Classes of reproductive toxicity:
  a. Male fertility
  b. Female fertility
  c. Parturition (toxicities affecting labor and delivery)
  d. Lactation
- Classes of developmental toxicity:
  a. Mortality
  b. Dysmorphogenesis (structural abnormalities)
  c. Alterations to growth
  d. Functional impairment (FDA, 2011a)

The final guidance goes on to describe a data integration process that is divided into three components: (1) all nonclinical toxicology and pharmacokinetic datasets; (2) nonclinical datasets without evidence of reproductive or developmental toxicity; and (3) nonclinical datasets with positive indications of reproductive or developmental toxicity (FDA,

2011a). See Appendix E-1 for FDA's schematics on these data integration approaches.

FDA states in the final guidance that recommendations for wording in labeling should be based on the results of the integration and assessment process and specific considerations leading to a risk conclusion should be provided, which may later be helpful in discussions between FDA reviewers and NDA and BLA applicants (FDA, 2011a).

According to a 2021 article published by members of FDA's Division of Urology, Obstetrics & Gynecology within FDA's Center for Drug Evaluation and Research in the *American Journal of Obstetrics and Gynecology*, there are three recognized categories of prescription product use by pregnant and lactating women:

1. The prescription product is approved specifically for an obstetrical or lactation-specific indication(s);
2. The prescription product is prescribed for an approved indication(s) in adults, which includes pregnant and lactating women (unless specifically contraindicated or there are warnings against such use), but the indication is not specific to an obstetrical, gynecological, or lactation-specific condition; and
3. The prescription product is prescribed during pregnancy or lactation off-label, where even if used for an approved indication(s), the product labeling expressly disallows or warns of product risks if administered during pregnancy or lactation and/or recommends against such use (Wesley et al., 2021). Note that under FDA's labeling regulations for prescription drug and biological products, FDA may require addition of a "specific warning" to a product's label "if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard" (21 CFR § 201.57(c)(6)(i)).

Prescription Products Approved Specifically for Obstetrical, Gynecological, and Lactation Indications

As of 2021, according to Wesley et al., there are only nine drugs that have been approved by FDA for marketing in the United States specifically for obstetrical indications, noting that this list does not appear to include products approved for all postpartum conditions, such as postpartum depression (Wesley et al., 2021).

1. Methergine (methylergonovine maleate) was approved in 1946 for use following delivery of the placenta, for routine management of uterine atony, hemorrhage, and subinvolution of the uterus,

and for control of uterine hemorrhage during the second stage of labor following the delivery of the anterior shoulder. Methergine's current labeling states it is used for the prevention and control of postpartum hemorrhage (Edison Therapeutics LLC, 2012).
2. Syntocinon (oxytocin nasal spray) is a supplemental NDA approved in 1968 for "initial milk let-down." Syntocinon has been discontinued from marketing (Wesley et al., 2021).
3. Pitocin (oxytocin for intramuscular or intravenous administration) was approved in 1980 for the "initiation or improvement of uterine contractions and to control postpartum bleeding" (Par Sterile Products, 2021).
4. Yutopar (ritodrine) was approved in 1980 to control premature labor. Yutopar has since been discontinued from marketing (Wesley et al., 2021).
5. Prepidil (dinoprostone) was approved in 1992 "for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction" (Pfizer, 2017).
6. Cervidil (dinoprostone) was approved in 1995 "for the initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor" (Ferring Pharmaceuticals, Inc., 2020).
7. Magnesium sulfate was approved in 1995 for the "prevention and control of seizures in preeclampsia and eclampsia, respectively" (Hospira, Inc., 2019).
8. Makena (hydroxyprogesterone caproate) was granted accelerated approval in 2011 "to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth." FDA withdrew the approval of Makena in April 2023 after the sponsor's postmarketing confirmatory study failed to verify clinical benefit (further discussed below) (Amag Pharmaceuticals, 2018).
9. Diclegis (doxylamine succinate and pyridoxine hydrochloride) was approved in 2014 "for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management" (Duchesnay Inc., 2022). The combination of doxylamine and pyridoxine had been marketed as Bendectin in the 1950s and approved for the same indication until its discontinuation in 1983 (Wesley et al., 2021).

FDA maintains a list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness, and this list was last amended on December 11, 2018 (21 CFR § 216.24). Of the products on this list, diethylstilbestrol had been prescribed to pregnant

women between 1940 and 1971 to prevent miscarriage, premature labor, and related complications of pregnancy, and was later used to stop lactation, but approval of the product was withdrawn based on its carcinogenic risks (NIH, 2015). Bromocriptine mesylate had been approved for preventing postpartum lactation, but FDA withdrew approval after concluding that "bromocriptine mesylate's risks of hypertension, seizures, and cardiovascular accidents outweighed the product's marginal benefit in preventing postpartum lactation, which can be suppressed without risk by using more conservative, nonpharmacological treatments" (FDA, 2018b).

More recently, on April 6, 2023, FDA announced the withdrawal of its approval of Makena (hydroxyprogesterone caproate injection) (FDA, 2023e). The product had been approved under the accelerated approval pathway to reduce the risk of preterm birth in women pregnant with one baby who had a history of spontaneous preterm birth. As a condition of accelerated approval, Makena's sponsor was required to conduct a confirmatory clinical trial to verify the predicted clinical benefit. However, this trial did not show improvement to the health of infants born to mothers treated with Makena and did not show that Makena reduced the risk of preterm birth, leading ultimately to its withdrawal from the market. There are known risks associated with Makena, and FDA determined that, given that effectiveness had not been shown, no level of risk was justified (FDA, 2023f).

A sponsor may elect to withdraw its own approved product from the U.S. market for a number of reasons, including commercial viability considerations unrelated to safety or effectiveness. Although FDA regularly updates the database of Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) to reflect drug and biological products that have been discontinued, there is not a central repository of voluntarily withdrawn products that is searchable by indication (i.e., to determine the number of pregnancy-specific products that have been withdrawn).

For devices, FDA's regulations at 21 CFR Part 884 set forth the classification of devices intended for obstetrical and gynecological use, including:

- Diagnostic devices used to evaluate the fetus: amniotic fluid sampler, fetal blood sampler and transabdominal amnioscope
- Devices used for monitoring pregnant patients: obstetric data analyzer, obstetric-gynecologic ultrasonic imager, fetal cardiac monitor, and fetal electroencephalographic monitor
- Obstetrical and gynecological prosthetic devices: cervical drain, vaginal pessary, fallopian tube prosthesis and vaginal stent
- Obstetric, gynecological, and fetal surgical devices: obstetric forceps and fetal head elevator

- Obstetrical and gynecological therapeutic devices: abdominal decompression chamber and perineal heater
- Various assisted reproduction devices (21 CFR Part 884

Devices classified under these regulations include Class I (general controls), Class II (special controls), and Class III (premarket approval) devices. Each regulation corresponds with a product code (or product codes) established by FDA, and there are numerous products listed under these codes in FDA's device premarket approval and premarket notification databases.

In our searches of FDA's labeling database, we did not identify any prescription drugs or biological products specifically indicated to treat lactating women; each of the labels returned in these searches with references to "lactation" or "lactating" referenced a contraindication, warning, or other safety information related to lactation.

With respect to prescription medical devices, FDA has regulations for nonpowered breast pumps (21 CFR § 884.5150), which are Class I devices, and powered breast pumps (21 CFR § 884.5160), which are Class II devices. There are 167 products listed in FDA's device database under the HGX product code for powered breast pumps.

Prescription Products Prescribed for Approved Indications in Adults

Where a prescription product is approved for use in adults, the product is also approved for use in pregnant or lactating women unless there is a clear contraindication or warnings against the product's use during pregnancy or lactation. This is because pregnant (and lactating) women are considered a subpopulation of the adult population and therefore, absent a contraindication or warnings against the product's use during pregnancy (or lactation), these women are not excluded from the approved population if a drug or biological product is approved for use in adults (FDA, 2018c). An example of such an approved product that is labeled to permit use during pregnancy or lactation with the opportunity to join a pregnancy exposure registry to monitor outcomes from use during pregnancy is Dupixent (dupilumab), which is indicated for several uses including asthma and moderate-to-severe atopic dermatitis (Regeneron Pharmaceuticals, Inc., 2023).

Prescription Products Prescribed for Unapproved Uses During Pregnancy or Lactation

When a prescription product is used in a manner not specified in FDA's approved labeling, such use is considered off-label. Although

manufacturers of prescription products are not permitted to promote their products for off-label uses, FDA has noted that "once FDA approves a drug, health care providers generally may prescribe the drug for an unapproved use when they judge that it is medically necessary for their patient" (FDA, 2018d). In the case of prescription products for use during pregnancy or lactation, a product would be considered as prescribed for an off-label use where the labeling of the product expressly contraindicates or warns against known risks of use during pregnancy or lactation. An example of such a drug would be Zocor (simvastatin), which is indicated for several uses including as an adjunct to diet to reduce low-density lipoprotein cholesterol (Organon LLC, 2023). The labeling for Zocor expressly warns of fetal harm and recommends against use during lactation.

Labeling

Overview

Labeling for prescription medicines is required for all FDA-approved prescription drugs and biological products and contains a summary of the essential scientific information needed for the safe and effective use of the medicine (21 USC § 355).

FDA's Physician Labeling Rule (the PLR), effective June 30, 2006, established FDA's first system for ensuring that product labeling identified the risks prescription drugs posed to pregnant women, fetuses, and breastfeeding infants (FDA, 2006b). The PLR established five pregnancy categories for sponsors to communicate the risks of adverse pregnancy outcomes posed by their products based on the information obtained during research and development:

1. Pregnancy category A was intended for products that had failed to demonstrate a risk to the fetus in the first trimester through adequate and well-controlled studies in pregnant women or animals (FDA, 2006b).
2. Pregnancy category B was intended for products in which animal reproduction studies had shown an adverse effect but further studies in pregnant women had failed to demonstrate a risk to the fetus within the first trimester (FDA, 2006b).
3. Pregnancy category C was reserved for products in which animal reproduction studies had shown an adverse effect on the fetus, without adequate and well-controlled studies in pregnant women, but where benefits from use of the product in pregnant women might be acceptable despite potential risks (FDA, 2006b).

4. Pregnancy category D was intended for products that had positive evidence of human fetal risk based on adverse reaction data but had a perceived positive benefit–risk ratio for pregnant women who used the product (FDA, 2006b).
5. Pregnancy category X was reserved for products with demonstrated fetal abnormalities or had exhibited positive evidence of fetal risk based on adverse event data from preclinical tests or clinical trials, and where the risk of product use by pregnant women clearly outweighed any perceived benefits (FDA, 2006b).

In addition to a "Pregnancy" section on a drug label, the PLR further required inclusion of information regarding labor and delivery and lactation. A "Labor and Delivery" section had to include information on the effects of the drug on the mother and the fetus, the duration of labor and delivery, and the effect of the drug on the future growth, development, and maturation of the child. For the "Lactation" section of the label there had to be a "Nursing Mothers" subsection that included information about the excretion of the drug in human milk and its effects on the nursing infant. Additionally, a description of any pertinent adverse effects observed in animal offspring had to be included in the labeling (FDA, 2006b).

In 2014, FDA amended its regulations through the finalization of its Pregnancy and Lactation Labeling Rule (the PLLR) (initially proposed in 2008), which created a consistent format for providing information about the risks and benefits of prescription drug and biological product use during pregnancy and lactation and by females and males of reproductive potential. For human prescription drug and biological products approved on or after June 30, 2001 (including products with labeling approved under the PLR), the PLLR required that the pregnancy categories A, B, C, D, and X be removed from the product labeling, and that the labeling be revised to include a summary of the risks of using a drug during pregnancy (Section 8.1 of the labeling), lactation (Section 8.2 of the labeling), and for females and males of reproductive potential (Section 8.3 of the labeling), a discussion of the data supporting that summary, and relevant information to provide health care providers and patients with the best available evidence to make informed decisions regarding the use of medications during pregnancy and lactation. Under the PLLR, all new prescription drugs and biological products approved by FDA after June 30, 2015, must comply with the PLLR (FDA, 2018e).

- Under the PLLR, Pregnancy Section 8.1 of a drug or biological product's labeling must include summaries of the pertinent available evidence providing information about the safety and use of the drug in pregnancy. Information on pregnancy exposure

registries, if available, including how to enroll or to obtain more information must also be included. A risk summary is also required that provides, as a narrative summary, a statement of background risk if there are data demonstrating that the product is systemically absorbed. This includes a separate summary based on human data, animal data, and pharmacology data that describes the risk of adverse developmental outcomes if such data are available. The risk summary section should also include background information regarding the risk of major birth defects and miscarriage in the U.S. general population. A "Clinical Considerations" section must detail disease-associated maternal and/or embryo–fetal risk, relevant dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal and neonatal adverse reactions, and labor and delivery information. Lastly, a "Data" section must describe the information and data used for the "Risk Summary" and "Clinical Considerations" sections (FDA, 2018e).

- Under the PLLR, "Lactation" section 8.2 of a drug or biological product's labeling must include a "Risk Summary" that summarizes the information about the presence of the drug or biological product in human milk, the effects of the drug or biological product and its active metabolite(s) on a breastfed child and the effects of the drug or biological product and its active metabolite(s) on milk production and excretion. In addition, there must be a risk–benefit statement that provides a framework for health care providers and lactating women to use when considering the benefits of breastfeeding to the mother and infant and the mother's need for treatment and benefits versus potential risks to the infant. Additionally, the "Risk Summary" should provide a risk–benefit statement if data demonstrate the therapeutic agent is systemically absorbed unless breastfeeding is contraindicated. Similar to the "Pregnancy" section, a "Clinical Considerations" section must include specific clinical information regarding ways to minimize exposure to the breastfed child and available interventions for monitoring or mitigating adverse reactions. A "Data" section must also describe the data that are the basis for the "Risk Summary" and "Clinical Considerations" sections (FDA, 2018e).
- Under the PLLR, a "Females and Males of Reproductive Potential" section 8.3 is required to be included in a drug or biological product's labeling when "pregnancy testing and/or contraception is required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects" (FDA, 2018e). Specific information about pregnancy testing, contraception, and infertility are also required, if applicable (FDA, 2018e).

Additionally, the PLLR requires statements acknowledging when data on any of the labeling requirements are not available or do not establish the presence or absence of drug- or vaccine-associated risk. Lastly, the PLLR requires the label to be updated to include clinically relevant information as it becomes available to prevent the label from becoming "inaccurate, false, or misleading" (FDA, 2018e).

FDA also issued draft guidance in December 2014, which it revised in July 2020, titled "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format," which provides detailed information for preparing the respective "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" subsections under the "Use in Specific Populations" section of a prescription drug or biological product's full prescribing information. The document provides general guidance on revising labeling and formatting as well as guidance for writing information within each specified PLLR subsection to help ensure that the narrative format provides meaningful information to health care providers. Under the PLLR, applicants must develop labeling to include the "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential" sections, and if a particular section of the PLLR required labeling information is not applicable, an applicant must submit information to FDA providing the rationale and justification for omitting subsections, headings, subheadings, or specific information required under the PLLR. The draft guidance reiterates that applicants are expected to update labeling as new information becomes available, including whether other sections of the labeling need to be updated (FDA, 2020b).

A study published in the *Journal of the American Medical Association Network Open* in 2020 indicated that, in a cross-sectional labeling analysis of 290 newly FDA-approved medications from January 2010 to December 2019 (focusing the review on new molecular entities and therapeutic products):

> All products submitted after June 20, 2015, were in compliance with the Pregnancy and Lactation Labeling Rule (PLLR); however, of those submitted between 2010 and 2015, 32.6 percent were not in PLLR format by the designated date of June 30, 2019. Human data on pregnancy and lactation were available in less than 20 percent of new product labeling (Byrne et al., 2020).

Only 31 of the products included human data related to pregnancy, but 260 products had animal data associated with pregnancy. When examining data related to lactation, 141 of the products had no data regarding medication safety. Only 8 products had human data related to lactation, but 143 had animal data related to lactation. The study also found that not all labels of products approved prior to the PLLR implementation

date had been converted to the PLLR format (and over one-third of these submissions still needed to be converted), therefore limiting the initial intent of the PLLR conversion to provide pregnancy and lactation risk summaries from available animal studies and clinical trials to aid health care providers when making prescribing decisions for pregnant or lactating patients (Byrne et al., 2020).

We conducted a search of FDA's labeling database (FDALabel), which is a web-based application used to perform customizable searches of human prescription drug and biological products, over-the-counter, and animal drug labeling documents. The source of FDALabel's data is FDA's Structured Product Labeling archive, which stores labeling documents submitted by manufacturers. As of February 21, 2023, there were 53,188 human prescription drug and biological product labeling in the database (FDA, 2023g). We identified approximately 4,500 prescription drug and biological product labeling results that include a "Section 8.1 Pregnancy" section as required by the PLLR. Of those, we identified approximately 980 prescription drug and biological product labeling results that include the phrase "human data" in "Section 8.1 Pregnancy" of the product labeling. Under the requirements of the PLLR as described above, a separate summary of human data that describes the risk of adverse developmental outcomes must be included if such data are available. Of the approximately 980 prescription drug and biological product labeling results described above, approximately 50 of them include the phrase, "There are no human data on the use of [Product] in pregnant women." Approximately 25 prescription drug and biological product labeling results included the phrase "pharmacokinetic" in "Section 8.1 Pregnancy" of the product labeling. Approximately 530 prescription drug and biological product labeling results include the phrase "pregnancy registry" in "Section 8.1 Pregnancy" of the product labeling.

Notable Comments to the PLLR

Following the publication of the proposed PLLR in 2008, FDA received comments from industry requesting that FDA clarify its expectations for the process and timing of updating the "Pregnancy" and "Lactation" subsections of labeling after new data become available, and the quantity and quality of data that necessitates a labeling update. FDA responded with the following:

> Because studies are not usually conducted in pregnant women prior to approval, most of the data regarding pregnancy and lactation will be collected in the postmarketing setting. Accordingly, in order that a drug product does not become misbranded, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading. Applicants are responsible for

> following the medical literature and also for updating labeling as new published and unpublished data become available (FDA, 2018e).

Some industry commentors were concerned about whether the PLLR was a way for FDA to impose mandates on sponsors to include pregnant women in research. For example, one industry commentor requested that FDA determine whether or not there would be a requirement for "additional activities from sponsors to collect such information [on pregnant women] and what tools [FDA] envision[ed] for such activities" (Novartis, 2008). The commentor noted:

> Whenever possible, animal data should be placed in context through label statements that (a) address the general applicability of the data to humans and (b) assess the overall strength of the data for a drug based on a comparison of results between treated and control animals and (c) discuss the consistency, or lack thereof, in results across animal species (Novartis, 2008).

In the commentor's opinion, this would eliminate manufacturer liability in instances where only animal data is used in labeling (Novartis, 2008).

On the other hand, some commentors wanted FDA to use the PLLR as a vehicle to mandate inclusion of pregnant women in clinical trials. An industry commentor noted that there was currently no regulatory requirement for sponsors to conduct clinical trials in pregnant women during the clinical development phase. This commentor further noted that it was industry practice to exclude pregnant women from preapproval clinical studies. Additionally, as there was no requirement that sponsors create pregnancy registries for any approved products (unless mandated by FDA as a postmarketing requirement; see "Postapproval Studies and Surveillance" section below), the commentor made the suggestion that in order to "encourage companies to more voluntarily and proactively obtain such information, FDA could request authority to provide incentives to industry to perform these studies and to collect more human data for labeling purposes" (Amylin, 2008). One comment further expounded upon this idea by stating that sponsors are unlikely to pursue pregnancy studies on their own and FDA is the only agency that could make pre- or postapproval studies with pregnant women a more common element of the approval and labeling processes (Public Citizen, 2008). A nonprofit organization focused on reproductive health also suggested FDA should use the new labeling guidelines as a way to encourage prescription drug sponsors to conduct studies on pregnant women (RHTP, 2008).

Incentives for industry to conduct studies with pregnant women were provided in commentary by health care providers, who suggested a 2- to 3-year extension of the drug's patent life span similar to pediatric labeling.

Their primary concern was that without an incentive, most labels would be written with the default statement that there was no human data on pregnancy and lactation and that animal studies would continue to be the standard (Manson and Kimmel, 2008).

Updates to Labeling Based on New Information

An application holder may submit a labeling supplement for FDA review at any time, but FDA has the authority to require (and, if necessary, order) labeling changes should it become aware of new safety information that FDA believes should be included in the product labeling (21 USC § 355(o)(4)). The term "new safety information" with respect to a drug, means:

> information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 355(o)(3) of this title), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of this title; or other scientific information deemed appropriate by the Secretary about: (A) a serious risk or an unexpected serious risk associated with the use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the [REMS] was required, or since the last assessment of the approved [REMS] for the drug; or (B) the effectiveness of the approved [REMS] for the drug obtained since the last assessment of such strategy (21 USC § 355-1(b)(3)).

As such, FDA may learn of new safety information through submissions from an application holder or through FDA's own monitoring activities. For example, new safety information may emerge through FDA's routine monitoring of its adverse event reporting systems; safety-related data in NDA, BLA, or IND submissions; inspections and investigations; medical literature submitted by application holders or external stakeholders (or identified by FDA staff); periodic safety updates or postmarket data submission from application holders; communications with foreign regulatory authorities regarding their analysis of adverse events associated with drugs approved in their countries; and meta-analyses of safety information, or new analyses of previously submitted information (FDA, 2013b).

According to FDA's final guidance titled, "Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act," FDA:

> expects that information that meets the standard of new safety information that should be included in labeling, thereby triggering safety labeling changes under section 505(o)(4), generally will include, but is

not limited to, information that would be described in new or revised language in the following sections of the prescribing information:

- Boxed warnings
- Contraindications
- Warnings and precautions
- Drug interactions
- Adverse reactions (FDA, 2013b).

Once FDA determines that new safety information should be included in product labeling, FDA can send a safety labeling change notification letter to the application holder, after which the application holder can either submit a supplement with proposed labeling changes to reflect the new safety information, or notify FDA that it does not believe the labeling change is warranted, and provide a rebuttal detailing why the applicant believes the changes are not necessary. FDA and the application holder can work to reach consensus on the proposed labeling, but if consensus cannot be reached, FDA can order the application holder to make the specified labeling changes (FDA, 2013b). If the application holder neither submits a supplement within 15 calendar days of the date of FDA's order, nor initiates dispute resolution within 5 calendar days of the date of FDA's order, the application holder will be in violation of section 505(o)(4) of the FD&C Act, which may result in enforcement actions (21 USC § 355(o)(4)(G); FDA, 2013b). Enforcement actions could include one or more of the following:

- Charges for introducing or delivering into interstate commerce a drug where the application holder is in violation of section 505(o)(1) of the FD&C Act (FDA, 2013b)
- Misbranding charges where the application holder for the drug violates safety labeling change requirements (FDA, 2013b; 21 USC § 352(z))
- Civil monetary penalties where the application holder violates safety labeling change requirements. These penalties increase if the violation continues more than 30 days after FDA notifies the application holder of the violation (FDA, 2013b; 21 USC § 333(f)(4)(A)).

Importantly, an application holder is expected to monitor the use of an approved product to facilitate submission of postmarket safety reports and required annual reports. For example, an annual report for an approved drug product should include (in addition to published clinical trials of a product in a given year), "reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant" (21 CFR § 314.81(b)(2)(vi)(a)). As noted above,

FDA may take this information into account when evaluating whether changes to a product's label are needed (FDA, 2013b).

In April 2005, FDA issued a final guidance titled, "Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies," which aims to help FDA staff evaluate human fetal outcome data generated after medical product exposures during pregnancies in order to develop product labeling that is useful to medical care providers who provide care to patients who are pregnant or planning pregnancy (see also "Labeling" section below). FDA acknowledges in this guidance that little may be known about a drug's or biological product's teratogenic potential at the time of submission of the application and that postmarketing surveillance of the product's use in pregnancy is critical to the detection of drug-induced fetal effects. Therefore, FDA states "It is important that FDA and sponsors routinely review all available data on drug exposure during pregnancy and work together to provide up-to-date product labeling that reflects what is known and not known about human fetal risk or lack of risk" (FDA, 2005).

In this reviewer guidance, FDA identifies seven factors for reviewers to consider when presented with human pregnancy data and faced with making a determination of whether and how the data should be included in product labeling:

- The first factor is background prevalence of adverse pregnancy outcomes. The final guidance states "a reviewer should consider whether there are enough exposures to demonstrate an increase in risk if such a risk exists. Any studies reporting no increase in the background rate of birth defects in exposed pregnancies can be viewed with skepticism unless the power of the study to detect or rule out a stated level of risk is also included" (FDA, 2005).
- The second factor is combined versus individual rates of birth defects, whereby reviewers should evaluate the overall rate of birth defects in the study population as well as rates of individual birth defects (FDA, 2005).
- The third factor is major versus minor birth defects (FDA, 2005).
- The fourth factor is timing of exposure, whereby reviewers should consider the timing and duration of exposure and their relationship to windows of developmental sensitivity as well as identify the frame of reference for the reported gestational age (i.e., time since conception) since:

  > Knowledge of the sensitive period for human target organ development facilitates optimal data interpretation. . . However, as a practical

matter the sensitive period for exposure to a drug, if there is one, is usually unknown. In situations where no clear toxicity has been identified, it is common to globally assess risk from first trimester exposures because that is the time of organogenesis (FDA, 2005).

The final guidance goes on to state that there are two potential sources of error in using this global approach: (1) sensitive time periods for a particular problem may make up a small portion of the first trimester; and (2) drug-induced fetal toxicities may not be limited to the first trimester or may produce abnormalities during more than one exposure window. The final guidance also states that evaluating the time of exposure is also important when assessing the power of a study (FDA, 2005).

- The fifth factor is intensity of exposure, whereby reviewers should consider the ability of a drug to cross the placenta and reach the fetus, including which stage of gestation such exposure occurs (FDA, 2005).
- The sixth factor is variability of response, whereby reviewers should consider that people differ in their responses to specific medications, for example:

Exposures during a sensitive time period known to increase the incidence of adverse pregnancy outcomes may do so only in a fraction of those infants exposed. . . . Although the effects of known teratogens are generally predictable from a population perspective, the nature and extent of effects are not necessarily possible to predict in individual patients under similar conditions. . . . Because of [maternal and fetal genotypic] variability, assessment of a drug's potential teratogenesis ought to consider the full range of birth defects. It is important to remember that the concept of variability extends not only to toxic responses, but also to baseline attributes of populations (FDA, 2005).

- The seventh factor is class effects, whereby:

Understanding the structure/activity relationships and pharmacological mode of action of a class of therapeutic agents in some circumstances can provide a prediction of the possible safety and efficacy of a new agent. However, such knowledge is generally not predictive of human teratogenesis. . . . While the introduction of a new product from a class of drugs with known human teratogenicity will solicit heightened scrutiny, it cannot be assumed that the product will also be teratogenic. Similar findings in the animal studies for the new product compared to the class would be cause for more concern, whereas clean animal data would lessen the concern (FDA, 2005).

With regard to the sources of human data on gestational drug exposures that FDA reviewers may receive, the final guidance states that "[information] on human gestational exposures will emerge during the postmarketing phase for virtually all drug products" and will come from a variety of sources, but "[f]or the most part, data will not be derived from controlled clinical trials, but from observational studies" (FDA, 2005). Human pregnancy outcome data is sent to FDA either directly by voluntary reports or via the sponsors as required by federal regulation (see "Postapproval Studies and Surveillance" section below). The final guidance states

> No single methodology can delineate the complete spectrum of adverse outcomes associated with prenatal exposure to a drug. Therefore, it is important to consider information from all available postmarketing surveillance sources to optimize detection and characterization of the reproductive effects of prenatal drug exposure (FDA, 2005).

FDA acknowledges that the most common types of data on human gestational exposures will likely come from case reports and epidemiological studies, including prospective cohort studies and pregnancy exposure registries, and retrospective birth defect registries and case control studies (FDA, 2005).

When conducting an overall assessment of postmarketing human data to determine whether there is an association between a gestational drug exposure and adverse pregnancy outcome, the final guidance states reviewers should consider evidence from all sources, including human data from case reports, epidemiology studies, and animal data, to determine the strength of the relationship. FDA further identifies six commonly used assessments that may be helpful to reviewers to apply to any accumulated data to test the possibility that an association is causal:

1. Strength of the association,
2. Consistency of the association,
3. Specificity of the association,
4. Appropriate timing,
5. Dose–response relationship, and
6. Biological plausibility (FDA, 2005).

Postapproval Studies and Surveillance

Overview

Any prescription drugs, biological products or medical devices manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by FDA, including, among other things, requirements related to manufacturing, record-keeping, reporting of adverse

experiences, periodic reporting, product sampling and distribution, and complying with FDA promotion and advertising requirements, among others.

As a condition of approval of an NDA for a drug or a BLA for a biological product, FDA may impose PMCs, PMRs, and/or a REMS program on the sponsor. The goal of PMCs, PMRs, and REMS programs are to better inform a "product's safety, efficacy, or optimal use" (FDA, 2016). PMCs involve preclinical studies or clinical trials that a sponsor agrees to conduct postapproval but are not legally required to be performed (FDA, 2016).

PMRs, however, are preclinical studies or clinical trials that a sponsor is required to conduct in order to comply with certain laws and/or regulations, or to assess a known serious risk related to the use of the drug, assess signals of serious risk related to the use of a drug, or identify an unexpected serious risk when available data indicate the potential for a serious risk (FDA, 2016). FDA may also impose PMRs on manufacturers of certain Class II or Class III medical devices that are approved by FDA. Examples of such requirements can include tracking systems; reporting of device malfunctions, serious injuries or deaths; and registering the establishments where devices are produced or distributed (21 USC § 360l; FDA, 2022b).

As of July 28, 2023, there were approximately 2,300 PMRs and PMCs listed in FDA's PMR and PMC database. Of these, around 2.6 percent involved preclinical developmental and reproductive toxicity ("DART") studies, around 0.2 percent involved clinical trials in pregnant individuals, around 1.2 percent involved clinical lactation studies, and around 8 percent involved a pregnancy registry or other prospective and/or retrospective observational study in pregnant and lactating individuals (FDA, 2023h). On FDA's public list of pregnancy exposure registries, which is a list of registries that are posted based on a sponsor or investigator's *request* to list their registry, there are 169 pregnancy exposure registries listed (FDA, 2023i).

FDAAA created section 505-l of the FD&C Act, which established FDA's REMS authority. REMS programs are designed to reinforce medication use behaviors and actions that support the safe use of medication and ensure that the benefits of a drug or biological product outweigh its risks. If a drug raises serious safety concerns, FDA has the authority to require a sponsor to participate in a REMS program, either as part of the product's approval, or postapproval if the drug or biological product later raises a safety issue (FDAAA, 2007; 21 USC § 355-l).

Current REMS Programs Specific to the Use of the Product in Pregnant or Lactating Women

As of August 25, 2023, there are 67 approved active REMS programs, 13 of which contain goals that are intended to, among other things,

mitigate risk of embryo–fetal toxicities in pregnant or lactating patients (FDA, 2023j). These 13 REMS programs are listed below:

1. Ambrisentan Shared System REMS ("The goal of the Ambrisentan REMS Program is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan"). Ambrisentan is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) (FDA, Ambrisentan Shared System REMS).
2. Bosentan Shared System REMS ("The goal of the Bosentan REMS Program is to mitigate the risk of hepatotoxicity and embryo–fetal toxicity associated with bosentan"). Bosentan is an endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) (FDA, Bosentan Shared System REMS).
3. Filspari REMS ("The goal of the FILSPARI REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with FILSPARI"). Filspari is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression, generally a urine protein-to-creatinine ratio ≥ 1.5 g/g (FDA, Filspari REMS).
4. Isotretinoin iPLEDGE Shared System REMS ("The goals of the isotretinoin risk evaluation and mitigation strategy are . . . to prevent fetal exposure to isotretinoin"). Isotretinoin is a retinoid indicated for the treatment of severe recalcitrant nodular acne in nonpregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater (FDA, Isotretinoin iPLEDGE Shared System REMS).
5. Lenalidomide Shared System REMS ("The goals of the Lenalidomide REMS are as follows . . . to prevent the risk of embryo-fetal exposure to lenalidomide"). Lenalidomide is a thalidomide analogue indicated for the treatment of adult patients with multiple myeloma (MM) in combination with dexamethasone; MM, as a maintenance following autologous hematopoietic stem cell transplantation; transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities; mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib; previously treated follicular lymphoma (FL) in combination with a rituximab product; and previously treated marginal zone lymphoma (MZL) in combination with a rituximab product (FDA, Lenalidomide Shared System REMS).

6. Macitentan Shared System REMS ("The goal of the Macitentan REMS Program is to mitigate the risk of embryo-fetal toxicity associated with macitentan"). Macitentan is an endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) (FDA, Macitentan Shared System REMS).
7. Mycophenolate and PC-Mycophenolate Shared System REMS ("The goal of the Mycophenolate REMS is to mitigate the risk of embryo-fetal toxicity associated with use of mycophenolate during pregnancy"). Mycophenolate is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart, or liver transplants, in combination with other immunosuppressants (FDA, Mycophenolate Shared System REMS; FDA, PC-Mycophenolate Shared System REMS).
8. Pomalidomide Shared System REMS ("The goals of the Pomalidomide REMS are as follows . . . to prevent the risk of embryo-fetal exposure to pomalidomide"). Pomalidomide is a thalidomide analogue indicated for the treatment of adult patients: in combination with dexamethasone, for patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy; and with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIV-negative (FDA, Pomalidomide Shared System REMS).
9. Pomalyst REMS ("The goals of the POMALYST risk evaluation and mitigation strategy are as follows . . . to prevent the risk of embryo-fetal exposure to pomalyst"). Pomalyst is a thalidomide analogue indicated for the treatment of adult patients: in combination with dexamethasone, for patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy; and with AIDS-related KS after failure of HAART or in patients with KS who are HIV-negative (FDA, Pomalyst REMS).
10. Qsymia REMS ("To inform certified pharmacies and patients of reproductive potential about: (1) the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy; (2) the importance of pregnancy prevention for patients of reproductive potential receiving Qsymia; (3) the need to discontinue Qsymia immediately if pregnancy occurs"). Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release,

an antiepileptic drug, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with a certain initial body mass index (FDA, Qsymia REMS).

11. Riociguat Shared System REMS ("The goal of the Riociguat REMS Program is to mitigate the risk of embryo-fetal toxicity associated with riociguat"). Riociguat is a guanylate cyclase stimulator indicated for the treatment of adults with: persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension ("CTEPH") (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class; and PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class, and to delay clinical worsening (FDA, Riociguat Shared System REMS).
12. Thalidomide Shared System REMS ("The goals of the Thalidomide REMS are as follows . . . to prevent the risk of embryo-fetal exposure to thalidomide"). Thalidomide is approved: in combination with dexamethasone for the treatment of patients with newly diagnosed MM; for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL); and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence (FDA, Thalidomide Shared System REMS).
13. Thalomid REMS ("The goals of the THALOMID REMS are as follows . . . to prevent the risk of embryo-fetal exposure to thalomid"). Thalomid is approved: in combination with dexamethasone for the treatment of patients with newly diagnosed MM; for the acute treatment of the cutaneous manifestations of moderate to severe ENL; and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence (FDA, Thalomid REMS).

As noted above, these REMS programs are designed (in part) to prevent or mitigate embryo-fetal toxicities, but we note that other products that are subject to REMS *may* be used by pregnant and lactating patients. For example, the Brixadi (buprenorphine) REMS program is intended "to mitigate the risk of serious harm or death that could result from intravenous self-administration" of the product, but the product, which is indicated to treat moderate to severe opioid use disorder, may be used by pregnant patients (and the prescribing information includes information on the "[l]imited data from trials, observational studies, case series, and case reports" in pregnant patients) (FDA, Brixadi REMS).

Section 505(o)(3) of the FD&C Act, added by section 901 of FDAAA, provides FDA with broad authority to require postapproval studies or

clinical trials (FDAAA, 2007; 21 USC § 355(o)(3)). The FDAAA expanded upon what postmarketing studies and clinical trials FDA can require in order to: (1) assess a known serious risk related to the use of the drug; (2) assess signals of serious risk related to the use of the drug; and (3) identify an unexpected serious risk when available data indicate the potential for a serious risk (21 USC § 355(o)(3)(B)). FDA also has the authority to require postapproval studies or trials if FDA becomes aware of new safety information (21 USC § 355(o)(3)(E)(ii); FDA, 2011b). Such authority has been interpreted to include FDA's ability to set the parameters for a sponsor's postapproval study or trial, which may include instructions on how to design the protocol, what type of population should be included, and for what indication (FDA, 2011b).

Additionally, sponsors of approved products may voluntarily conduct postapproval studies to gain additional experience from the treatment of patients in the therapeutic indication.

Section 505(o)(3)(E)(ii) of the FD&C Act requires a sponsor to "periodically report," and in any event at least annually, on the status of preclinical studies or clinical trials, regardless of whether or not the sponsor was required to conduct a clinical trial or study as part of a PMR, or voluntarily chose to do so. A sponsor must report on the preclinical study or clinical trial's status to comply with this section (21 USC § 355(o)(3)(E)(ii). The status report should include a timetable for completion of specific target goals, along with a status update of the study or trial (FDA, 2011b).

Postapproval Studies in Pregnant and Lactating Women

In FDA's 2011 Guidance, "Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act," FDA describes examples of PMRs and PMCs. PMRs may include "observational pharmacoepidemiologic studies designed to assess a serious risk associated with a drug exposure or to quantify risk or evaluate factors that affect the risk of serious toxicity, such as drug dose, timing of exposure, or patient characteristics" (FDA, 2011b). In general, such a study would involve a thoughtfully designed protocol and include a control cohort, although some studies may not include a control group if there is reason not to. Data for these types of studies may come from institutional electronic medical records, health insurance claim data, as well as registries. These observational studies may aid in (1) assessing the relative risk of a serious adverse event occurring with use of a particular drug or biologic, (2) identifying certain risk factors that make the occurrence of a serious adverse event among a particular patient population more likely, and (3) obtaining data over a significant period of time, which may help identify rare serious adverse events, among others.

In regard to pregnancy, such observational studies may aid in informing pregnancy or child outcomes following drug exposure, in comparison to a group that has not been exposed to the drug product. Other types of PMRs may include meta-analyses to evaluate a safety endpoint and clinical trials with a safety endpoint designed to analyze a serious risk raised by FDA under section 505(o)(3). Examples of PMCs may include drug and biologic quality studies, pharmacoepidemiologic studies reviewing the natural progression of a disease, surveillance and observational pharmacoepidemiologic studies, or clinical trials involving a primary endpoint that seeks to further evaluate a drug or biological product's efficacy (FDA, 2011b).

Pregnancy Registries

Pregnancy registries are a common study design that may be used to collect safety data in the postapproval setting and can help inform decision making among health care providers and their patients (FDA, 2019c). Pregnancy registries involve the prospective enrollment of women who have been exposed to a drug or biologic product and are usually followed through delivery and postpartum to evaluate the effects of exposure on the newborn. Such registries may be led by a sponsor, government, or institution; they may be product specific or cover multiple products, can involve multiple institutions and other collaborative stakeholders, and include more than one country. They are an important and potentially powerful safety tool to use owing to their ability to prospectively capture detailed patient data over a long period of time. Because of difficulties in enrollment and retention, however, pregnancy registry data often may not carry enough statistical power to assess safety of drug and biological products during pregnancy (FDA, 2019c).

In 2002, FDA released its final guidance, "Establishing Pregnancy Exposure Registries," that provided recommendations on how to design and implement a pregnancy registry in the postapproval setting (FDA, 2002). Although it has since been withdrawn with the release of FDA's 2019 draft guidance (discussed below), the 2002 guidance laid a foundation for sponsors to more seriously consider the regular use of well-designed pregnancy registries in the postapproval setting (FDA, 2019c).

In 2014, FDA held a 2-day public meeting that included experts studying birth defects from academia, professional organizations, industry, and patient advocacy groups to discuss the development, design, and conduct of pregnancy registries, along with other types of study designs (FDA, 2019d). FDA also performed a review of pregnancy registries, as well as assessed pregnancy registry design methods and issues related to recruitment and retention (Gelperin et al., 2017).

Additionally, the 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to address the unmet needs of pregnant and lactating women in research, and in its 2018 report outlined recommendations to the secretary of HHS and Congress. PRGLAC's report noted that, to date, one of the most commonly used methods for obtaining information on pregnant women was through registries. In its recommendations, it noted that in order to maximize registry potential, the creation of a "user-friendly website for registry listing, developing registry standards with common data elements, and facilitating transparency and access to the data" was needed (PRGLAC Task Force, 2018; NIH, 2022). The report also emphasized that the design of disease- or condition-focused registries, as opposed to product-specific registries, would provide for more streamlined data collection into a single registry, but acknowledged that this would "require substantial coordination, collaboration, and funding mechanisms" (PRGLAC Task Force, 2018).

In 2019, FDA issued its draft guidance, "Postapproval Pregnancy Safety Studies." This guidance describes three postapproval approaches (which can be addressed in any one or combination of approaches) to use in assessing drug safety in pregnant women who have been exposed to drug or biological products: (1) pharmacovigilance; (2) pregnancy registries; and (3) complementary data sources. Based on an approach's strengths and limitations and application to a particular drug or biological product, FDA may recommend or require a particular approach or combination of approaches to be used by a sponsor for such drug or biologic product (FDA, 2019c).

A pharmacovigilance approach includes a compilation of data on adverse pregnancy outcomes in order to detect a safety signal or signals. Exposure reports received by the sponsor and FDA, medical literature involving case studies, and other specific case reports may be used as sources. As noted in the draft guidance, factors to evaluate may include: (1) a detailed synopsis of the adverse pregnancy outcome; (2) a complete account of the exposure, inclusive of the medication, its dose, frequency, route of administration, and duration; (3) the gestational age at which the exposure likely occurred; (4) a comprehensive medical history of the mother, including use of concomitant medications, supplements, etc.; and (5) any exposures to known or suspected environmental teratogens. In general, however, pharmacovigilance may not allow for a "conclusive assessment," often because of underreporting and a lack of complete information from such exposure reports, which may only capture a specific point in time (FDA, 2019c).

A large portion of the draft guidance discusses recommendations for the design and implementation of pregnancy registries. Pregnant women who have been exposed to a drug or biological product may volunteer to

participate in a registry during their pregnancy and be followed through delivery. Because a pregnancy registry follows a pregnant woman over the course of her pregnancy and following the birth of her newborn, it may allow assessment of "maternal, obstetrical, fetal, and infant outcomes, including pregnancies that do not result in a live birth" (FDA, 2019c). Although the draft guidance points to a number of strengths in using pregnancy registries, it highlights some limitations for such registries: (1) analyses may result in insufficient statistical power in detecting associations for rare pregnancy outcomes; (2) registries may not address more specific or rare congenital malformations, congenital anomalies, and birth defects; (3) there may be significant challenges to recruitment and retention; and (4) the data from a registry alone may not be able to adequately assess the safety of a drug or biological product taken during pregnancy (FDA, 2019c).

FDA may also require that a lactation study to capture potential drug exposure data during breastfeeding be added to a pregnancy registry. Such lactation data is gathered to assess the safety of drugs and biological products that women may take while breastfeeding, which may or may not have been taken while pregnant (FDA, 2019c).

The draft guidance also provides detailed recommendations for registry design, as well as advice on how to address recruitment and retention challenges. Importantly, FDA notes that sponsors should collaborate with health care providers, as well as with other potential stakeholders, such as existing registries, patient advocacy groups, medical societies, and other relevant organizations to help promote pregnancy registry recruitment. FDA also notes that sponsors may wish to collaborate with other sponsors on multiproduct registries and find other ways to create collaborative registries that reduce the administrative burden and potential duplicity of information in such registries. Although FDA actively lists pregnancy registries on its Office of Women's Health website, it does not "endorse any registry and is not responsible for the content of registries listed on [FDA's] web page" (FDA, 2019c).

FDA also provides guidance on the potential duration of a pregnancy registry. FDA recommends that pregnancy registries collect data until there is sufficient information gathered to meet the registry's scientific objective(s), or conversely, if the registry is not able to collect sufficient information to meet its objectives, it should consider discontinuing the registry. If other, more efficient methods become available that allow the sponsor to obtain the same information that was being gathered from the registry, FDA notes the sponsor should also consider disbanding the registry (FDA, 2019c).

Finally, FDA discusses complementary studies that may be used alongside pregnancy registries that may be conducted to address "specific effects"

of a drug or biological product during pregnancy. These studies may be retrospective in their design and use secondary data sources, such as electronic health records, population-based surveillance, and national registries or registers (FDA, 2019c).

Public comments to FDA's 2019 draft guidance from pharmaceutical industry organizations, women's health research societies and organizations, academia, and other stakeholders have generally commented that pregnancy registries were overly discussed in the 2019 draft guidance and did not provide enough guidance on alternative available methods. In particular, because pregnancy registries alone may not provide sufficient data, commentors noted that considerations for other study methods are equally important to address. In addition, some commentors asked that more specific recommendations on the data elements for pregnancy outcomes and common exposure information be implemented across publicly funded and privately sponsored pregnancy registries (PhRMA, 2019). One commentor also noted that the draft guidance was silent on paternal or male sexual partner exposure (Medications in Pregnancy and Lactation Special Interest Group, 2019). Another comment encouraged FDA to also consider premarket actions that could further include pregnant and lactating women in clinical trials, as opposed to being focused entirely on the postapproval setting (Society for Maternal-Fetal Medicine, 2019).

On September 18, 2023, FDA, together with the Duke-Margolis Center for Health Policy, hosted a public workshop titled, "Optimizing the Use of Postapproval Pregnancy Safety Studies," which included discussions of designs of postapproval pregnancy safety studies for drug and biological products and experiences with implementing such studies, as well as considerations for further development of a framework that describes how data from different types of postapproval pregnancy safety studies might optimally be used when it has been determined that such data should be collected (FDA, 2023k).

Other Initiatives

FDA's Sentinel Initiative, a multistakeholder and collaborative initiative that "aims to develop new ways to assess the safety of approved medical products" has also been assessing infant and maternal outcomes from use of drug and biologic products (FDA, 2023l). In 2019, FDA established the Sentinel Innovation Center and Community Building and Outreach Center that has sought to "find[] ways to extract and structure information from electronic health records," which may help address some of the concerns that commentors voiced to the 2019 draft guidance regarding difficulties in linking maternal and infant health records (FDA, 2023m). The Sentinel Initiative has a page dedicated to pregnancy on FDA's website, stating that "developing and refining methods to assess medical product utilization,

safety, and effectiveness during pregnancy is a focus of FDA's Sentinel System" (FDA, 2023n). One such initiative is using a statistical data mining tool, known as TreeScan, to "assess maternal and infant outcomes, test signal identification methods in a pregnancy setting, and evaluate methods performance using older drugs with relatively well-characterized safety profiles" (FDA, 2023o). These research initiatives include mother–infant electronic health record linkage, validation of an algorithm to identify stillbirths, and an algorithm to identify the gestational age of live births, to name a few (FDA, 2023p,q,r).

In addition, FDA is continuing the development of the "FDA MyStudies App," an open-source mobile application software designed to facilitate direct patient input of real-world data that can be linked to electronic health data, thereby supporting traditional clinical trials, observational studies, and registries (FDA, 2023s; FDA, 2018f). A pilot study was conducted by the Harvard Pilgrim Health Care Institute through the FDA Sentinel Initiative Catalyst program that used this app to help identify "medication exposures, other risk factors, and pregnancy outcomes" among women from the Kaiser Permanente Washington health system (FDA, 2023s; Wyner, et al., 2020).

As the Society for Women's Health Research (SWHR) pointed out in its comment to the 2019 draft guidance, real-world evidence is another valuable method of data collection. The National Institutes of Health (NIH) created the PregSource research study, which was concluded on April 30, 2023 and will have data available by August 27, 2023 (NIH, 2023a). PregSource was a mobile app that allowed pregnant women to enter data, such as their weight, sleep, and mood (NIH, 2023b). SWHR noted in its comment that although this type of data may not evaluate medical treatments, collection of real-world evidence during pregnancy, which may include medications taken during pregnancy, is nevertheless important data to gather and should not be overlooked (SWHR, 2010).

CONSIDERATIONS AND OPPORTUNITIES FOR THE FUTURE

Based on our review of FDA's authorities, guidance, and policies that are available on the development and commercialization of prescription products for use by pregnant and lactating women, we have identified the following discrete considerations and opportunities that, if implemented by FDA, may support regulatory initiatives relating to the development and commercialization of prescription products for use by pregnant and lactating women:

- Assess the effect of FDA's 2018 draft guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials,"

which is intended to provide guidance to industry on how and when to include pregnant women in clinical trials for drugs and biological products.

- Continue to support inclusion of pregnant and lactating women in clinical trials through strengthened recommendations in new or updated clinical trial diversity-related guidances.
- Issue new or updated guidances relating to formal meetings with FDA to proactively inform sponsors that FDA meeting packages should address why pregnant and lactating women are either included or excluded in clinical trial design plans in order to support FDA meeting discussion or written feedback from FDA on sponsor inclusion or exclusion plans for these populations.
- Issue new or updated guidance or guidelines for IRBs reviewing and providing oversight for clinical trials involving pregnant and lactating women, specifically clarifying what is required by "additional safeguards" that must be included in clinical trials to protect the rights and welfare of subjects who are pregnant under 21 CFR § 56.111(b), which can be an impediment for sponsors, especially for those conducting multisite studies.
- Together with NIH, expand existing search result filtering functionalities within ClinicalTrials.gov, especially as it relates to eligibility criteria, to ensure pregnant and lactating women interested in identifying available clinical research opportunities that permit enrollment of pregnant and lactating women are able to efficiently locate such studies. Consideration should also be given to establishing a set of pregnancy- and lactation-specific terms that sponsors and investigators should use to describe their clinical trials, particularly with respect to the description of inclusion and exclusion criteria, when listing their clinical trials on ClinicalTrials.gov. For example, without a standardized set of descriptors (i.e., defining the eligible pregnancy population by gestational age or trimester), sponsors employ varying terms to describe the stage of pregnancy where such women are eligible, thereby making it challenging for pregnant women to identify clinical trials for which they may be eligible.
- Make publicly available statistics on PLLR compliance, including the percentage of approved prescription products with human clinical data supporting their PLLR-compliant product labeling.
- Issue new or updated safety labeling and/or PLLR labeling guidances to prospectively describe circumstances where the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of product labeling should be updated when new information becomes available where such failure could cause the labeling to become inaccurate, false, or misleading.

- Recommend, or by expansion of law, require that all sponsors or investigators who establish a pregnancy registry list such registry on FDA's List of Pregnancy Exposure Registries.
- By expansion of law, develop a new marketing exclusivity period that may be awarded to sponsors or application holders who obtain and submit human clinical data to FDA evaluating their prescription products in pregnant and lactating women.

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21 CFR § 50.25(b)(1), Elements of informed consent.
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21 CFR § 216.24, Drug products withdrawn or removed from the market for reasons of safety or effectiveness.
21 CFR § 312.20, Requirements for an IND.
21 CFR § 312.23(a)(8), IND content and format.
21 CFR § 314.81(b)(2)(vi)(a), Other postmarketing reports.
21 CFR § 812.20, Applications.
21 CFR Part 884, Obstetrical and Gynecological Devices.
21 USC § 333(f)(4)(A), Violations related to devices.
21 USC § 352(z), Postmarket studies and clinical trials; new safety information in labeling.
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APPENDIX D-1

Schematics of Complete Data Integration Processes from FDA's 2011 Final Guidance for Industry on Reproductive and Developmental Toxicities—Integrating Study Results to Assess Concerns

Figure A is applicable to all nonclinical toxicology and pharmacokinetic datasets and should be used for any of the endpoints of reproductive or developmental toxicity.

Figure B. Decision Tree for Endpoints with No Signal

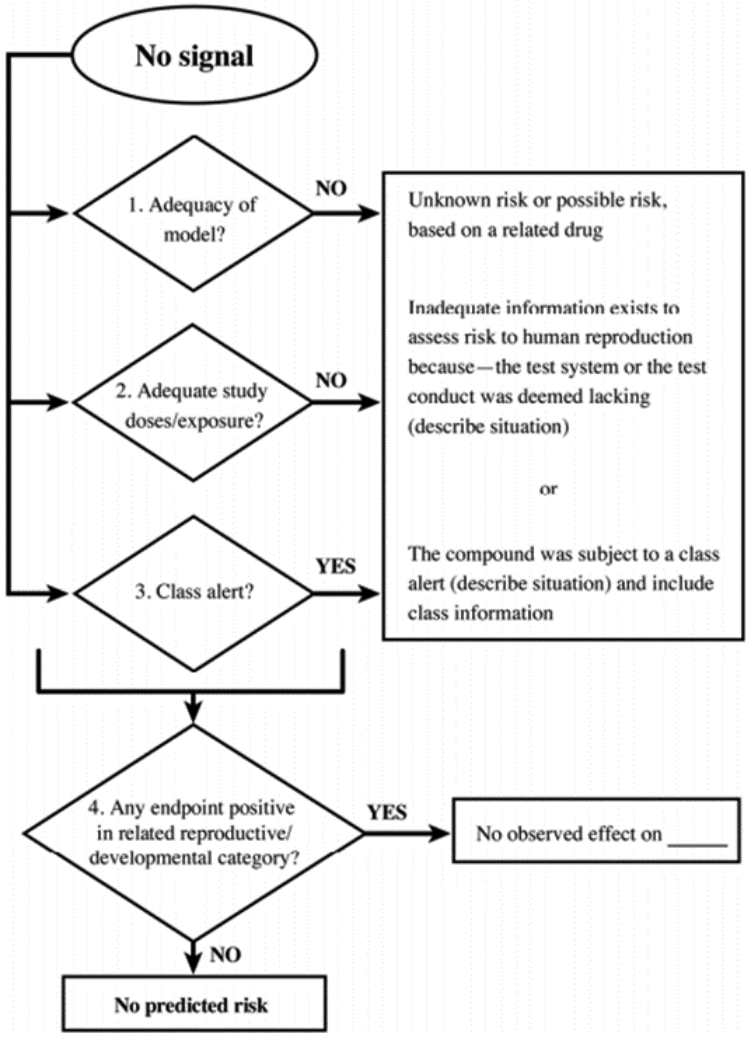


Figure B is applicable to nonclinical toxicology and pharmacokinetic datasets where there is no positive signal for an endpoint of reproductive or developmental toxicity.

Figure B. Decision Tree for Endpoints with No Signal

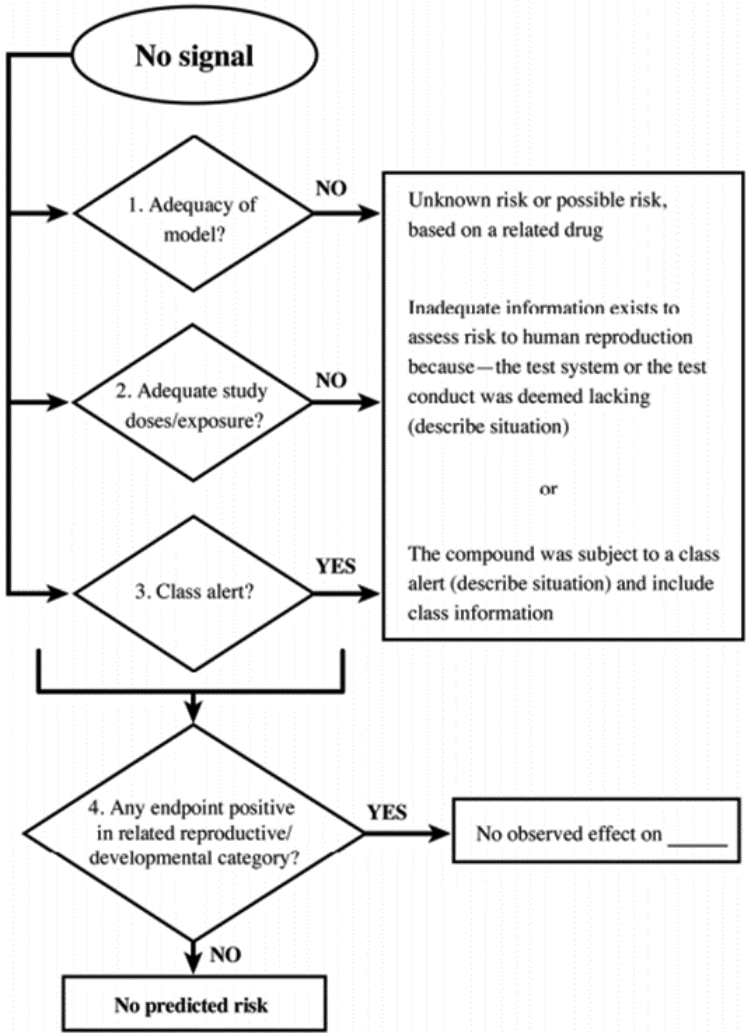
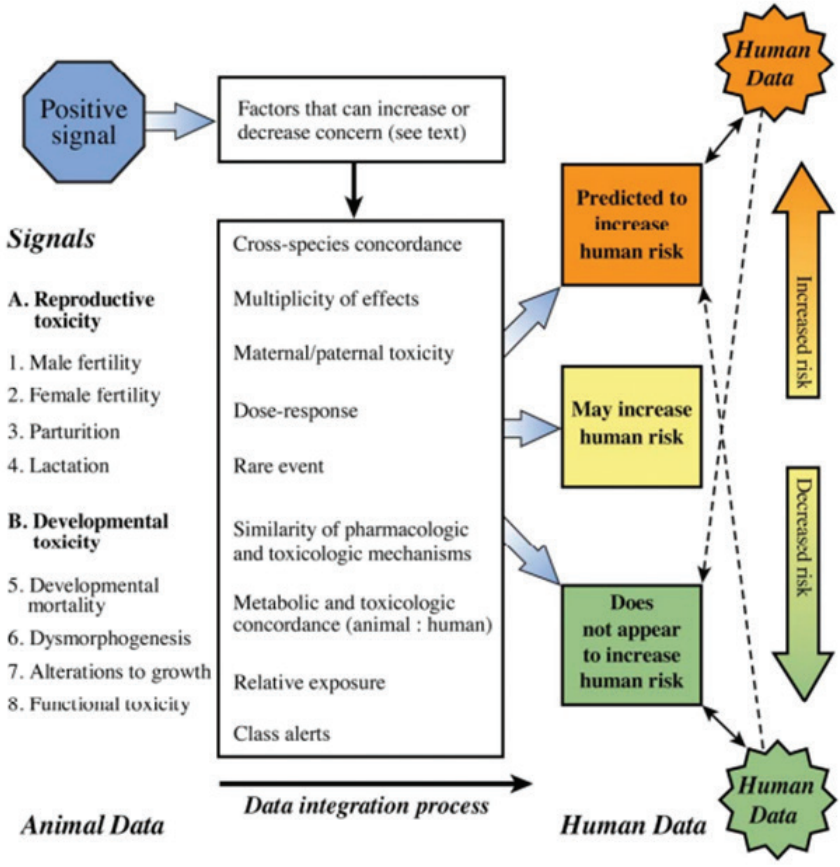


Figure C is applicable to nonclinical toxicology and pharmacokinetic datasets with positive indications of reproductive or developmental toxicity.

Figure C. Integration of Reproductive or Developmental Toxicities with a Positive Signal



E

The Impact of *Dobbs v. Jackson Women's Health Organization* on Clinical Research with Pregnant and Lactating Persons

AUTHOR

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This report assesses the current and potential future consequences on clinical research with pregnant and lactating persons of the U.S. Supreme Court's 2022 decision in *Dobbs v. Jackson Women's Health Organization* (*Dobbs v. Jackson women's health organization*, 2022). The report is organized as follows: the first section introduces the issue and key terms. The second section– describes the general legal and regulatory landscape governing clinical trials and human subjects research, including a section focused specifically on the laws, regulations, and policies governing research involving pregnant and lactating persons. The third section unpacks some of the likely consequences of *Dobbs* on clinical research involving pregnant and lactating persons. The final section concludes by suggesting mechanisms that may mitigate the possible effects of *Dobbs* on clinical research involving pregnant and lactating persons.

The consequences of *Dobbs* in the clinical and research context remain in flux, making much of this document predictive and somewhat speculative. The consequences predicted in this document are not guaranteed to transpire. Federal and state laws surrounding abortion and reproductive health care continue to evolve, making it difficult to predict consequences with a high degree of certainty. Nevertheless, such uncertainty requires that all stakeholders remain flexible and informed of ongoing changes in the law so they can adapt accordingly.

SUMMARY

The *Dobbs* decision is unlikely to have a significant effect on research involving lactating persons. The effect of *Dobbs* and the state laws and regulations that have transpired after the constitutional right to abortion was overruled in *Dobbs* focus primarily on activities that occur during the *prenatal* period, such as abortion and fetal harm. Yet *Dobbs*—and the laws that have or may flow from the decision—are likely to make research involving pregnant persons more difficult, costly, and rife with legal uncertainties and risks. Despite the incremental progress in recent years towards greater inclusion of pregnant persons in clinical trials, *Dobbs* places that progress in jeopardy.

In the context of clinical research, the most immediate effect will be experienced by sponsors of clinical trials studying various methods of medication or procedural abortion. But as this report describes, the effect of *Dobbs* on research involving pregnant women may extend beyond clinical trials studying medication and procedural abortions and affect the study of other reproductive medicines and technologies or perhaps even any drug that has the potential to cause fetal harm or spontaneous abortion. The consequences may affect trial sponsors, individual investigators, participants, participants' health care providers, and funders of clinical research. If *Dobbs* has consequences for broader swaths of research, the consequences may be felt more broadly by the health care system and society.

If clinical research involving pregnant persons becomes more difficult in the wake of *Dobbs*, pregnant persons themselves may experience short- and long-term harms. Although antiabortion policy makers typically defend their positions as necessary to prevent fetal harm or death, the collateral consequences of those laws may defeat their very purpose, resulting in a continued lack of evidence and knowledge about how medical products affect pregnant persons and their fetuses. As stated by Dr. Catherine Spong, a professor and chair of the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical Center, although researchers think they are protecting pregnant persons and their fetuses by excluding them from trials, "what [they] are doing is making them more vulnerable. Now you are going to be treating them based on no data and no evidence. By not including them, you are almost to the point of experimenting each time" (Balch, 2022).

A pregnant person's need for medication does not disappear during pregnancy. Pregnant persons will, and often must, continue to take medications during pregnancy. Ninety percent of women report taking some type of medicine during pregnancy, and seventy percent report taking at least one prescription medicine. From 1976 to 2008, women's use of prescription medicines during their first trimester of pregnancy increased by

more than 60 percent. Yet problematically, many of the medications used have not be studied in pregnant persons (Prevention, 2023). Data and evidence are needed to ensure medications are safe for use during pregnancy. Clinical trials help provide that data, yet they often remain legally and ethically difficult to perform, issues that have been compounded by *Dobbs*. Relatedly, harms may result if pregnant persons avoid necessary and beneficial medical interventions during pregnancy because of lack of evidence, a situation that transpired during the COVID-19 pandemic with the COVID-19 vaccines (Lamptey, 2022).

Many of the questions and considerations raised in this report do not yet have clear answers. There are many new and emerging issues that must be considered in the clinical trials community in terms of how the *Dobbs* decision may affect clinical research in the United States and whether there are ways to minimize the potential consequences. There remains much to learn about the full effect of *Dobbs*, and it may be years before we know the true scope of the harm.

INTRODUCTION

Key Terms

This report focuses on the effect of *Dobbs* on clinical research involving pregnant and lactating persons. It does not address the effects on the broader population of persons capable of pregnancy, although research on that population will likely also be affected by *Dobbs*. Key terms used in this report include:

- *Lactating persons*—persons feeding an infant with their own breast milk after giving birth.
- *Medication abortion*—abortion caused by medications (e.g., pills) that are intended to be used to induce an abortion. Example: mifepristone, approved by the U.S. Food and Drug Administration (FDA) in combination with misoprostol to induce an abortion through 10 weeks gestation.
- *Persons capable of pregnancy*—persons with a uterus in which a fertilized egg can be implanted.
- *Pregnant persons*—a human person at any stage of pregnancy (i.e., postimplantation of an egg that has been fertilized by sperm). This report aims to use gender-neutral language whenever possible. Abortion is often framed as a "women's" issue, but transgender, nonbinary, and gender-nonconforming people may also become pregnant and need abortions. The term *woman* or *women* may be used, however, particularly where the sources use that terminology.

- *Procedural abortion*—abortion caused by a medical procedure that removes the embryo or fetus and the placenta from the pregnant person's uterus. Sometimes called *surgical abortion*.
- *Stillbirth*—death of a fetus after 20 weeks gestation (Prevention, 2022).
- *Spontaneous abortion*—the loss of a pregnancy at less than 20 weeks gestation. Often referred to as a miscarriage (Dugas and Slane, 2022).

Background: Abortion in America

On June 24, 2022, the U.S. Supreme Court issued its decision in *Dobbs v. Jackson Women's Health Organization*, thereby overturning *Roe v. Wade*, 1973, and *Planned Parenthood of Southeastern Pennsylvania v. Casey, 1992*. In short, *Dobbs* held that the Due Process Clause of the Fourteenth Amendment does not protect the right to abortion. Without constitutional protection, the states now possess even greater freedom to ban or severely restrict access to abortion care. *Dobbs* does not, however, foreclose the possibility of courts finding that another provision of the U.S. Constitution protects the right to abortion, nor does it prevent the federal government or individual state governments from enshrining the right to abortion in federal laws, state laws, or state constitutions.

Other constitutional theories, such as federal preemption, also provide a strong argument against restrictive state laws, particularly with respect to mifepristone, a drug approved by FDA for use in combination with misoprostol for medication abortion. The Supremacy Clause, found in Article VI, Clause 2, of the U.S. Constitution, provides that the "Constitution, and the Laws of the United States which shall be made in Pursuance thereof. . .shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." This language provides the foundation for the doctrine of federal preemption, under which federal law supersedes conflicting state laws. Essentially, the argument is that FDA's authorization and regulation of mifepristone—which is done pursuant to federal law—preempt state laws banning the use of mifepristone or enacting greater restrictions on its use than provided for under FDA regulation.

As of July 2023, there are numerous cases working their way through the courts relying, at least in part, on preemption. Two cases getting much attention involve conflicting rulings issued by two separate federal court judges. The first, *Alliance for Hippocratic Medicine v. FDA, 2023,* was issued on April 7, 2023, by Judge Matthew Kacsmaryk in the U.S. District Court for the Northern District of Texas. Judge Kacsmaryk issued a preliminary

injunction that suspended FDA's 23-year approval of mifepristone. He also endorsed the view that a previously dormant, 150-year old law—the Comstock Act—"plainly forecloses mail-order abortion." The Biden Administration appealed this ruling to the Fifth Circuit Court of Appeals. In a 2-1 decision, the U.S. Court of Appeals for the Fifth Circuit blocked the portion of Judge Kacsmaryk's ruling that overturned FDA's 2000 approval of mifepristone but allowed the reimposition of restrictions on mifepristone previously lifted by FDA. These reimposed restrictions include limiting mifepristone's approved use to 7 (instead of 10) weeks' gestation and requiring that patients pick up the medication in person (i.e., prohibiting the use of mail pharmacies). The Biden Administration again appealed, this time to the U.S. Supreme Court, which temporarily blocked the decisions of both lower courts, returning the case to the Fifth Circuit. The Supreme Court ruled that access to mifepristone will remain unchanged for the duration of the lawsuit, which is expected to ultimately make its way back before the Supreme Court (Rights, 2023). Despite the back-and-forth nature of the courts' actions, the Supreme Court's recent ruling means that access to mifepristone remains unchanged and the drug is still considered approved by FDA.

The second, and conflicting, ruling was issued that same day—April 7, 2023—in the U.S. District Court in the Eastern District of Washington by Judge Thomas O. Rice. This case— *Washington v. FDA, 2023*—was filed by 18 attorneys general from 17 states and the District of Columbia and challenges FDA's decision to impose restrictions on the dispensing and prescribing of mifepristone through what is known as a Rick Evaluation and Mitigation Strategy (REMS). Essentially, this case is the mirror image of the Texas case, arguing that FDA must *remove* restrictions rather than reimpose restrictions or ban the drug. In this case, the court ordered FDA to maintain the current availability of mifepristone in the 17 states and the District of Columbia.

As of this writing, attempts to protect abortion through federal legislation have largely been unsuccessful, and while some states have recognized the right to abortion in their state constitutions or laws, many states have also banned or severely restricted access to abortion. The legality and accessibility of abortion in the United States remain in a constant state of flux. The overall absence of any current federal protection for abortion means that a person's access to abortion depends in large part on their geographic location, financial resources, and ability to travel to a state where abortion care remains available.

Yet even before *Dobbs*, states used many direct and indirect mechanisms to restrict abortion, often with the Supreme Court's blessing. As the number and severity of restrictions mounted, their cumulative effect often rendered abortion out of reach for many pregnant persons (Whelan, 2023).

Dobbs has magnified the challenges associated with accessing safe abortion care, even in life-threatening situations. The *Dobbs* decision has—and will continue to—affect the lives of many Americans—forcing some to make agonizing choices, eliminating choices for many others, and placing many in danger. Many consequences have already been seen, yet it will likely take years to understand the full consequences of *Dobbs*.

Background: Fetal Personhood

When the Supreme Court decided *Roe v. Wade* in 1973, it rejected the argument by the state of Texas that a fetus is a "person" within the language and meaning of the Fourteenth Amendment. In overturning *Roe*, the Supreme Court in *Dobbs* did not address the issue of fetal personhood, thus leaving the question open for states to decide. As the term implies, fetal personhood laws grant the rights of personhood to the unborn, sometime from the moment of conception or detection of a fetal heartbeat.

The state of Georgia, for example, enacted the Living Infants Fairness and Equality (LIFE) Act in 2019. Among other things, this law defines an unborn child as "a member of the species *Homo sapiens* at any stage of development who is carried in the womb." The law qualifies this in various sections, granting certain rights and privileges solely to unborn children with a "detectable heartbeat," which can occur as early as 6 weeks gestation. Although most fetal personhood laws are being passed with an intent to target and ban abortion, the implications are broader, both explicitly and implicitly. Explicitly, under Georgia law, for example, an unborn child with a detectable human heartbeat can now be claimed as a dependent on income taxes. (Living infants Fairness and Equality (LIFE) act, 2019). Implicitly, contraception and treatments for infertility such as in vitro fertilization may be affected (Manninen, 2023). As described further below, fetal personhood laws may also affect research involving pregnant persons.

The remainder of this report focuses on the regulation and performance of clinical research, and specifically focuses on an often-overlooked consequence of *Dobbs*: the effect of the decision on clinical research with pregnant and lactating persons. The vast majority of clinical trials do not involve the explicit performance or study of medication or procedural abortions, and state restrictions on abortion have thus far not addressed clinical trials explicitly. Nevertheless, abortion bans, restrictions, and other similar laws that prioritize the prevention of fetal harm or pregnancy loss from any cause may pose difficulties for clinical trials involving pregnant and lactating persons. This is attributable, in part, to the broader effects of antiabortion laws. Antiabortion laws and policies have and may lead to the possibility of any fetal harm or death (e.g., spontaneous abortion,

stillbirth, in utero exposures resulting in fetal anomalies that may prompt the pursuit of an abortion, premature labor that could result in neonatal death) being viewed with suspicion and potentially prosecuted as an illegal abortion, feticide, or homicide.

This report concludes that the effect of *Dobbs* on research involving pregnant persons will likely be far greater than the effect on research involving lactating persons. Barriers remain to including lactating persons in clinical trials, but there is little reason to believe that *Dobbs* will significantly increase the difficulties or add new ones. The same cannot be said for pregnant persons.

LAWS AND REGULATIONS GOVERNING CLINICAL TRIALS AND HUMAN SUBJECTS RESEARCH

This section first provides a brief overview of the legal and policy landscape for clinical trials and human subjects research generally. It then describes the rules and policies specific to research involving pregnant and lactating persons.

General Regulatory Landscape of Clinical Trials and Human Subjects Research

Federal Laws and Regulations

The Federal Policy for the Protection of Human Subjects—often referred to as the "Common Rule"—was published in 1991 and revised in 2018. The Common Rule was heavily influenced by the Belmont Report, which was issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Protections, 2022).

The Common Rule applies to human subjects research conducted or supported by one of the federal departments or agencies that have codified the policy, such as the Department of Health and Human Services (HHS). HHS, for example, has codified the Common Rule in the Code of Federal Regulations (CFR) at 45 CFR Part 46, with four subparts (Subparts A–D). Many nongovernmental entities have also elected to apply parts of the Common Rule to their research, regardless of whether they receive funding from one of the relevant agencies (Protections, 2022).

Clinical trials that produce data that will be submitted to FDA in support of product approval by FDA must be designed, conducted, analyzed, and reported in compliance with a separate set of regulations, codified at 21 CFR Parts 50 and 56. These regulations are similar but not identical to the Common Rule. In the Fall of 2022, two notices of proposed rulemaking

were issued to harmonize the human subject protection regulations of HHS and FDA (Administration, 2022).

Additionally, many clinical trials are conducted by hospitals or academic medical centers (AMCs), which are subject to the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Health Information Technology and Economic Clinical Health Act of 2009 (HITECH Act). At a high level, these laws outline the lawful use and disclosure of protected health information (PHI). Hospitals and AMCs that are subject to these laws must comply with their requirements, which establish conditions under which PHI may be used or disclosed for research purposes.

State Laws and Regulations

In addition to federal laws and regulations, states may also enact laws that affect clinical trials, including laws that regulate the conduct of human subjects research and those that relate to informed consent, age of consent, legal representatives, and government notification, among other things (*Protection of human subjects in medical experimentation act*, 2023). Some states also impose specific consent, confidentiality, and privacy requirements on particular types of activities, such as those involving genetic, mental health, substance use, or reproductive health information (Acheson and Halaiko, 2023). State laws often provide *greater* protection for the confidentiality of health information than HIPAA, and thus are not preempted by HIPAA.

Institutional Policies

Many institutions, including AMCs, have policies that mirror or supplement federal and state regulations governing clinical trials and human subjects research. At a minimum, institutions must adhere to federal and state requirements, but they can also supplement them with their own institutional policies. For example, the Catholic University of America does not conduct research, nor does it allow students to be placed in off-campus academic situations (e.g., internships) that involve human embryonic stem cells or other primary human fetal or embryo cells (America, 2020).

Regulatory Landscape for Research Involving Pregnant and Lactating Persons

In addition to the general laws and regulations governing clinical research discussed previously, various rules and policies have been issued by HHS and FDA concerning research involving pregnant and lactating persons.

These policies were not developed in a vacuum. Paternalism and concerns for potential adverse effects on pregnant and lactating persons, persons capable of pregnancy, and fetuses have played a significant role in the development of federal regulations governing clinical research involving these populations. Clinical research and its regulation have long been affected by the abortion debate (Liu and Mager, 2016; Waggoner and Lyerly, 2022). As explained by Waggoner and Lyerly, (2022), "The basis of research protections as we know them was developed during [the 1970s]," the same decade when *Roe v. Wade* was decided. *Roe*, which held that the Due Process Clause of the Fourteenth Amendment of the U.S. Constitution protects a person's liberty to choose to have an abortion (subject to some limitations that increase as the pregnancy progresses), provided a key backdrop to the deliberations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which considered the issue of research involving the fetus. The tensions are obvious: conversations about concerns for fetal life and well-being were occurring in tandem with debates about abortion, women's right to choose, and women's autonomy more generally.

Catalysts for protectionist research policies included the thalidomide and diethylstilbestrol (DES) tragedies exposed in the 1960s. Thalidomide, used primarily as a sedative and treatment for nausea in early pregnancy, caused a rare set of deformities in children born to women who used the drug, including severe limb malformations. DES, widely prescribed in the 1940s and 1950s to prevent miscarriages, has now been linked to adenocarcinoma in the children of women who took DES during pregnancy (Institute of Medicine Committee on and Legal Issues Relating to the Inclusion of Women in Clinical, 1994). Controversy over the Dalkon Shield, an intrauterine device, also likely played a role. Women claimed it failed to protect them from unwanted pregnancies, ectopic pregnancies, septic abortions, miscarriages, birth defects, excessive bleeding and cramping, pelvic inflammatory disease, infertility, or death (Menkel-Meadow, 1998; Parekh et al., 2011). Ironically, these tragedies, which resulted in part because the products were *not* studied in pregnant persons, caused even more resistance to test medications in pregnant populations. The response to these tragedies may have exacerbated the problems by causing underrepresentation of pregnant and lactating persons, thereby increasing knowledge gaps.

The formalization of these protectionist policies began in 1975, with the promulgation of federal regulations that restricted pregnant women from being involved in research unless specific criteria were met. The restrictive policies were broadened further when FDA issued "General Considerations for the Clinical Evaluation of Drugs" in 1977 ("the 1977 Guidelines"). The 1977 Guidelines set forth acceptable approaches to

clinical trials with investigational drugs and recommended that "females who are pregnant, or at risk of becoming pregnant" (i.e., of childbearing potential), be excluded from early-stage research (i.e., Phase I trials).

The 1977 Guidelines also stated that women of childbearing potential "may be included" in later stage, Phase III, studies "[i]f adequate information on efficacy and relative safety has been amassed during Phase II" studies and if animal reproductive studies have been completed. For women of childbearing potential enrolled in a study, the 1977 Guidelines recommended that pregnancy tests be performed and that the women be advised about suitable methods of contraception. According to Waggoner and Lyerly (2022), these policies "promulgated the notion of the fetus as uniquely vulnerable to research harms."

The 1977 Guidelines did not provide much guidance regarding whether lactating persons may or may not be included in clinical trials. Instead, the 1977 Guidelines simply stated that "[e]xcretion of the drug or its metabolites in the milk of lactating women should be determined, when feasible, prior to the use of the drug in nursing mothers."

Over time, the restrictions have been relaxed. In 1993, FDA published new guidelines and withdrew the restrictions on the participation of women of childbearing potential in early clinical trials (e.g., Phase I) (Administration, 1993). These revisions were a response to growing concerns that the drug development process did not produce adequate information about the safety and efficacy of drugs in women. FDA itself acknowledged that the 1977 Guidelines were viewed as "rigid," "paternalistic," and "overprotective"; left "virtually no room for the exercise of judgment by responsible female research subjects, physician investigators, and [investigational review boards (IRBs)]"; and denied "young women the opportunity available to young men and older women to participate in early drug development research." FDA did not, however, require inclusion of women in general or women of childbearing potential, and recognized that drug companies and/or IRBs may not change their restrictions.

In 1998, FDA sought to address the problem further by issuing a Final Rule amending its regulations pertaining to Investigational New Drug Applications (INDs) and New Drug Applications (NDAs). Among other things, this Final Rule amended FDA regulations to require sponsors of NDAs to include in their applications analyses of safety and effectiveness data for certain subgroups, including gender. FDA has the authority to refuse to file an NDA that lacks such data (21 cfr 314.101(d)(3), 2020). In 2000, FDA promulgated another Final Rule that gives FDA the authority to place a trial for a life-threatening disease or condition on clinical hold if the sponsor excludes men or women only because of reproductive potential (Administration, 2000). This rule only applies to trials for a life-threatening disease or condition in which the subjects

have the disease or condition; it does not apply to trials only involving healthy volunteers or for diseases or conditions that are not considered "life-threatening."

Many of the regulations discussed previously referred broadly to "women of childbearing potential." In 2018, FDA addressed the specific subgroup of pregnant persons when it issued draft guidance titled "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials" (Administration, 2018). The draft guidance is intended to "support[] an informed and balanced approach to gathering data on the use of drugs and biological products during pregnancy through judicious inclusion of pregnant women in clinical trials and careful attention to potential fetal risk" (Administration, 2019, 2020). In addition to these and other changes, the FDA Office of Women's Health (OWH) was established by congressional mandate in 1994, with a mission to, among other things, promote the inclusion of women in clinical trials and the implementation of guidelines concerning the representation of women in clinical trials and completion of sex or gender analysis.

Another set of regulations that applies to research involving pregnant and lactating persons is found in Subpart B of the HHS regulations entitled "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research." Furthermore, the provisions of Subpart D are applicable to research with children, including viable neonates, and therefore may be implicated in research involving lactating persons who may transfer some of a medication they take to a breastfeeding child.

Despite this progress, much work remains. The COVID-19 pandemic brought the issue into the spotlight once again. Despite the increased risk of severe illness in pregnant persons, along with other risks such as preterm birth, initial trials of the COVID-19 vaccines excluded pregnant and lactating women. As a result, pregnant and lactating persons were left to decide whether to get the vaccine without much, or any, evidence of its safety for pregnant persons. Health care providers were likewise left in the dark. This lack of data likely decreased vaccine uptake in pregnant persons, as lack of trust in COVID-19 vaccines and concern about safety and side effects are predictors of low vaccine uptake (Galanis et al., 2022). Data now show that low vaccine uptake among pregnant persons resulted in harm to pregnant persons and fetuses. Unvaccinated pregnant persons had higher rates of maternal mortality, and SARS-CoV-2 infection in pregnant persons has been associated with higher risks of admission to the neonatal intensive care unit, intrauterine fetal death, perinatal mortality, preeclampsia, and preterm labor (Grunebaum and Chervenak, 2022; Watanabe et al., 2022). For lactating persons, administration of the COVID-19 vaccine has resulted in temporary decreased milk supply, an effect that was not discovered until the vaccine was being widely used,

due to the exclusion of lactating persons in the initial clinical studies (Kachikis et al., 2021).

Waggoner and Lyerly (2022) emphasize that most research regulations in the United States were developed after 1973, and thus during a time when abortion was legal. Waggoner and Lyerly "fear that the changing legal landscape in the U.S. threatens progress in addressing key evidence gaps in the care of women and pregnant persons. Just as *Roe* had consequences for the evolution of research with these populations, so, too, will its reversal."

DOBBS: THE CONSEQUENCES AND IMPLICATIONS FOR CLINICAL RESEARCH

As noted in the second section of this document, much progress has been made in recent years toward recognizing the importance of and improving knowledge about how medical products, such as drugs, affect pregnant and lactating persons, who were historically excluded from clinical trials. Yet, much work remains to mitigate the harms that result from the lack of evidence and knowledge that remains. *Dobbs* jeopardizes the incremental progress made and risks stalling further progress.

This section describes how the *Dobbs* decision has or may affect clinical research involving pregnant and lactating persons. Some of the consequences listed are more likely than others to transpire. Moreover, an important caveat to the findings of this report is that at this time, much remains unknown about the full impact of *Dobbs*. With time, the scope of the consequences of *Dobbs* will become clearer.

Lactating Persons

The direct result of *Dobbs* is greater restrictions on access to abortion throughout the United States. The goals of some abortion opponents, however, extend beyond merely returning the legality of abortion to the states, and include complete elimination of abortion in the United States and the legal recognition of fetal personhood.

The goals of abortion opponents are thus focused principally on *prenatal* activities and outcomes, which will primarily affect pregnant persons but not lactating persons (unless that lactating person is also pregnant). In short, *Dobbs*, and the antiabortion movement more generally, are about *fetal* protection. The movement does not focus on protections for newborns no longer in utero.

A main reason why lactating persons are excluded from clinical research is because of concerns about how medications may affect nursing infants. Laws that restrict access to or eliminate abortion or laws that protect fetuses should not affect clinical trials on lactating persons.

Pregnant Persons

In contrast to lactating persons, *Dobbs* is likely to affect clinical research involving pregnant persons. This section outlines how *Dobbs* and the restrictions, bans, and fetal protection laws promulgated as a result of that decision may make clinical trials involving pregnant persons more difficult and may increase the risk of liability of performing such trials.

Trials in Progress

Sponsors of trials in progress will need to consider whether any of these trials need to be halted or whether protocols will need to be amended. In making these decisions, sponsors will need to consider the location of their trial sites, whether and how the site's abortion laws have changed since *Dobbs*, and whether and how that affects the performance of their trial or collection of specific types of data. Sponsors should also consider whether there is a need to obtain new consent from participants to address legal restrictions on abortion access given a change in law after enrollment and initial consent.

The frequent, often back-and-forth changes being seen in abortion laws, particularly as some laws are being challenged in courts, means that sponsors should engage experienced legal counsel to ensure their trials remain compliant with changing state laws, which remain in a constant state of flux. Given the evolving nature of state abortion laws, sponsors should also consider establishing a process that requires periodic review of their trials in conjunction with any new or amended state or federal laws and regulations.

Limitations on What Can Be Studied

Clinical trials studying abortion drugs, methods, and services will experience the most direct and significant consequences. The studies will be subject to the same state requirements as those services when provided at the clinical level. Thus, if there is a ban on providing medication abortion or procedural abortions in the clinical context in a state, there will also be a ban on providing abortion in the research setting in that state. This will make studying new methods of medication abortion more difficult and even impossible in some states. Studying medicines like mifepristone, as well as other drugs known to increase the risk of pregnancy loss for nonabortion purposes, will also be legally difficult.

As noted by Sugarman et al., "fear of legal risks associated with facilitating an abortion, or uncertainty about the rapidly evolving legal status of abortion, might leave researchers reluctant to obtain rigorous data

on pregnancy, possibly including adverse pregnancy-related outcomes." If that occurs, data will be incomplete and less valuable to researchers and society more generally.

The Comstock Act

The Comstock Act was not mentioned in *Dobbs*, but recent court cases involving medication abortion attempt to bring back to life this relatively dormant antivice law. The Comstock Act of 1873 made it illegal to send "obscene, lewd or lascivious," "immoral," or "indecent" publications through the mail. The Act also made it a misdemeanor for anyone to sell, give away, or possess an obscene book, pamphlet, picture, drawing, or advertisement (*An act for the suppression of trade in, and circulation of, obscene literature and articles of immoral use*, 1873).

The Act's prohibitions include writings or instruments pertaining to contraception and abortion. Specifically, the Act bans the mailing of articles, including drugs and medicines, or things "designed or intended" to procure an abortion. The Comstock Act's prohibitions extend not only to the United States Postal Service, but also to "any letter carrier" or "common carrier," including the United Parcel Service or Federal Express.[1] The Supreme Court overturned the Act's restrictions on contraception in the 1965 case *(Griswold v. Connecticut, 1965)* and Congress subsequently amended the law to remove the reference to contraception. Furthermore, in December 2022, the Department of Justice (DOJ) issued an opinion stating that the Comstock Act:

> does not prohibit the mailing of certain drugs that can be used to perform abortions where the sender lacks the intent that the recipient of the drugs will use them unlawfully. Because there are manifold ways in which recipients in every state may lawfully use such drugs, including to produce an abortion, the mere mailing of such drugs to a particular jurisdiction is an insufficient basis for concluding that the sender intends them to be used unlawfully (Schroeder, 2022).

Thus, under this interpretation, because mifepristone has been approved by FDA for termination of pregnancy through 10 weeks gestation, the Comstock Act does not prevent the mailing of that drug if the intent is to use the drug to terminate a pregnancy as approved by FDA.

Even while *Dobbs* did not address or involve claims relating to the Comstock Act, the decision paved the way for new and ongoing litigation involving the Comstock Act. For example, litigation has been brought

[1] Mailing obscene or crime-inciting matter; and Importation or transportation of obscene literature. 18 U.S.C. 1461-62.

challenging FDA's approval of mifepristone, one of the drugs approved by FDA in the medication abortion regimen. Among other claims, this lawsuit claims that the Comstock Act prohibits the mailing of mifepristone. This lawsuit and prominent antiabortion lawyers are focused on how the law applies to the mailing of abortion drugs. The broadest interpretations being put forward by some opponents of abortion would mean that even tools and medical instruments that facilitate abortion procedures that are shipped in the mail to clinics and other facilities would be caught in the Comstock Act's net (Sneed, 2023).

Should enforcement of a broader reading of the Comstock Act transpire, there could be serious implications for clinical trials. The significance, however, will depend largely on how expansive an interpretation is adopted. Many drugs and devices are designed in ways that could, if used in particular ways, cause an abortion. Such a broad view would implicate most, if not all, clinical trials. A narrower interpretation, which only affects drugs and devices specifically *intended* to cause an abortion, would implicate far fewer clinical trials—primarily those involving drugs and devices being studied for the precise purpose of causing a medical or procedural abortion. As a federal law, its enforcement would, for all intents and purposes, prevent the study of any drug intended to induce an abortion because it is almost certain that a clinical trial would require some of the drugs to be shipped through the mail system.

Clinical Trial Location

Dobbs may affect the location of clinical trial sites, which may detrimentally effect the diversity of clinical trials.

Current guidelines from the Council for International Organizations of Medical Sciences (CIOMIS) state: "Research with pregnant women must be conducted only in settings where these women can be guaranteed access to safe, legal abortion." Sponsors following those guidelines would thus not be able to perform clinical trials in the many states that have banned or severely restricted abortion (CIOMIS, 2016).

According to Waggoner and Lyerly (2022), "Trial participants may desire termination of pregnancy in the rare circumstance where participation in the study is associated either with fetal harm or with prolonging a pregnancy where maternal health is in danger (e.g., severe preeclampsia)." If abortion is not available to these participants, they may have to drop out of the trial.

If clinical trials cannot be held in certain states, the diversity of clinical trials may decrease, making it more difficult for sponsors to achieve adequate racial, ethnic, and socioeconomic diversity. According to Sugarman

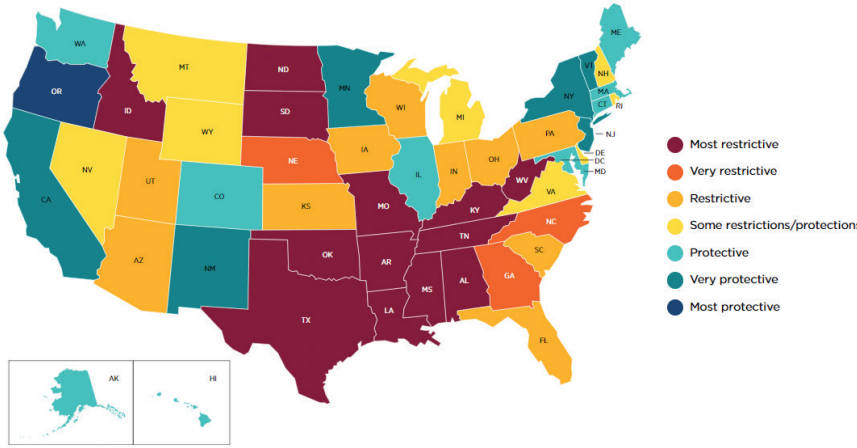

FIGURE E-1 U.S. abortion policies and access after *Dobbs* (as of July 25, 2023)
SOURCE: Institute, 2023c.

et al. (2023), sponsors must consider whether the risks of performing trials at certain sites outweigh the benefits, but that "such decisions should not be taken lightly because such a choice obviates the opportunity for people who can become pregnant to participate in research and generate locally relevant data."

Many of the southern states with the most severe abortion laws in the country are also densely populated by people of color, including the majority of Black Americans, as depicted in Figure E-1 (Abrams, 2023; Bureau, 2021). Sponsors will continue to be able to conduct trials in states with large populations of people of color, such as California, which currently protects access to abortion, but the pool of participants will be far smaller. According to the 2020 Census, for example, roughly 3.3 million Blacks live in Georgia, whereas approximately 2.2 million Blacks live in California. The 2020 census data show that southern states like Georgia, Louisiana, Mississippi, Alabama, and South Carolina have some of the highest percentages of Black populations. These same states have all banned or severely restricted access to abortion as of the date of this report; some of these bans are currently blocked by court order (*Times*, 2023) (see Table E-1).

Informed Consent Issues

Sponsors will need to consider whether and how their informed consent procedures need to be amended to describe the risks of pregnancy loss; availability of abortion or contraception; possible effects on a fetus; and the risks of pregnancy information and outcomes being

TABLE E-1 Ten States with Highest Percentage of Black or African American Alone[2] Population (2020 Census)

State or District	Black or African American Alone (2020 Census)	Abortion Policies
District of Columbia	41.4% (285,810 people)	No bans
Mississippi	36.6% (1,084,481 people)	Abortion banned with very limited exceptions
Louisiana	31.4% (1,464,023 people)	Abortion banned with very limited exceptions
Georgia	31.0% (3,320,513 people)	Abortion banned at 6 weeks
Maryland	29.5% (1,820,472 people)	Abortion banned at fetal viability (~24–26 weeks gestation)
Alabama	25.8% (1,296,162 people)	Abortion banned with very limited exceptions
South Carolina	25.0% (1,280,531 people)	Abortion banned at 22 weeks gestation (6-week ban on hold while legal challenges continue)
Delaware	22.1% (218,899 people)	Abortion banned at fetal viability (~24–26 weeks gestation)
North Carolina	20.5% (2,140,217 people)	Abortion banned after 12 weeks
Virginia	18.6% (1,607,581 people)	Banned starting at third trimester

NOTE: Red rows are states that have banned abortion at or less than 6 weeks. The yellow row indicates an abortion ban after 12 weeks.
SOURCE: Bureau, 2021; Institute, 2023b; *Times*, 2023.

recorded, reported, or accessed by state officials. Participants should also be informed of whether there is a potential risk of prosecution or other legal liability should their fetus be harmed or should they decide to terminate a pregnancy after a positive pregnancy test so they can continue the trial or if their fetus is harmed by the product being tested.

If sponsors are conducting trials in states where abortion is banned or severely restricted, sponsors should also strongly consider providing this information explicitly to participants during the informed consent process. For example, if pregnancy is an exclusion criterion, sponsors should consider whether to inform participants that if they become pregnant during the study and want to get an abortion so they can remain in the trial, it may be difficult for them to access abortion care, meaning they will have to drop out of the study.

[2] Black or African American alone includes respondents who reported only one response to the race question in the U.S. Census.

Sponsors should also consider whether they intend to provide participants with information about how to access an abortion should they become pregnant during the course of the trial and they want to obtain an abortion so they can remain in the trial (if pregnancy is an exclusion criterion). In states where abortion is banned or severely restricted, there could be legal liability for doing so, which could affect the pregnant persons, the sponsor, and study staff. Such risks are more acute where the language of the law suggests that those who "aid and abet" an abortion can be held liable. For example, Texas law provides civil liability for any person who "knowingly engages in conduct that aids or abets the performance or inducement of an abortion" that is otherwise illegal under Texas law (*Civil liability for violation or aiding or abetting violation*, 2021).

The potential expansion of fetal personhood laws made possible by *Dobbs* may also affect informed consent for trials that include pregnant persons. Even though clinical trials enrolling pregnant persons remain relatively rare, they have increased in recent years amid the push to expand medical knowledge about how drugs affect pregnant persons and fetuses. Thus far, the pregnant person has the legal and ethical authority to consent to their participation in research (assuming they meet the other criteria for giving informed consent). Where fetal personhood laws exist, the issue of consent may become more complicated.

For example, if a state considers a fetus a person under the law, sponsors will need to determine whether *two* separate consents must be obtained before a pregnant person can enroll in a clinical trial. If two consents are needed, sponsors must also consider whether the pregnant person, as the "parent" of the fetus, will have the authority to consent to the fetus's participation, just as the parent of a born minor child would. This raises the question of whether the fetus's other biological or legal parent should also have a role in the consent process.

The consent process may be complicated if the pregnant person wants to enroll in the clinical trial but the other parent is concerned about the fetus and refuses to consent to the fetus's participation in the research. Subject to some exceptions, federal regulations already require the consent of the father "if the research holds out the direct benefit solely to the fetus" (Services, 2001). But in situations where the research also or solely holds out a possible direct benefit to the *pregnant person*, and not the fetus, the father's consent is not explicitly required. Yet in a post-*Dobbs* world, more states may consider adopting fetal personhood laws or state laws requiring the other parent's consent when a pregnant person enrolls in a clinical trial. If a state's law considers a fetus a person, and thus analogous to a *child*, sponsors may have to comply with the requirements specific to consent for a *child's* involvement in clinical trials. Under federal regulations, IRBs may require the permission of both parents for certain types of

research involving children(Services, 45 C.F.R. § 46.408, 2001). A specific state's personhood laws will matter, however, because these same federal regulations provide that "children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, *under the applicable law of the jurisdiction in which the research will be conducted*" (Services, 1983).

Documentation and Privacy Concerns

Background Complicated privacy concerns have long been an issue for research involving pregnant persons, often stemming from the state's purported interest in protecting fetal life. For example, an IRB at the University of South Dakota encountered such privacy issues when the IRB was presented with a protocol for a five-state study of fetal alcohol syndrome that involved identifying and monitoring women who drink during pregnancy. South Dakota law, however, requires officials to report potentially abusive behavior toward a fetus, which includes drinking alcohol. Investigators were unable to offer research participants a certificate of confidentiality or other privacy protection because of state law. As a result, women who volunteered for the study were at risk of being reported to state officials and potentially facing legal repercussions because of their substance abuse while pregnant. Ultimately, the governor's office wanted the study to proceed because its objectives involved a positive intervention—helping pregnant persons with drinking problems with educational interventions intended to help them maintain sobriety. Under the state's decision, the women would still be reported to the state, but the state would take no action against any individual participants of the study (Advisor, 2003).

Post-*Dobbs* The breadth of privacy issues may increase as states propose and enact news laws aimed at preventing abortion, protecting fetal life, and policing the bodies and choices of pregnant persons. The current legal environment, including its instability, underscores the importance of protecting the confidentiality of all information about trial participants' pregnancies and use of abortion services.

Dobbs may affect how researchers record pregnancies among subjects and whether and how that information is protected from disclosure. In many clinical trials involving nonpregnant subjects, initial and periodic pregnancy tests are a standard part of trial protocol. These tests are deemed necessary when a trial's protocol requires exclusion of pregnant persons, yet they may also detect early pregnancies that would have otherwise gone unnoticed because of high rates of first trimester miscarriages. A positive pregnancy test during the course of a trial is

typically considered a "reportable event," so participants must be willing to report their pregnancies and feel secure doing so, particularly if they are considering an abortion. According to Aoife Brennan, CEO of Synlogic, Inc., *Dobbs* "is forcing people involved in clinical research to rethink something as simple as pregnancy tests, which had once been taken for granted, and plan for the possibility that research sponsors and study sites will be required to share pregnancy and outcome data with state officials" (Skerret, 2022). Sugarman et al. (2023) agree, stating: "The simple fact that a research participant is not pregnant nor has given birth, but a test indicates that they were pregnant during research, could put them at risk of legal action."

For the last 4 decades, the Centers for Disease Control and Prevention (CDC) has partnered with states to collect aggregate statistics about abortion. States are not required to submit their abortion data to CDC, but the majority do report. Moreover, even though states are not required to submit their abortion data to CDC, the majority of states require hospitals, facilities, and physicians to submit regular reports to the state with various information about abortions performed. Some of these states also require reporters to provide some information about the reason the person sought an abortion (Institute, 2023a). Some states have attempted to go further, proposing laws that would require reporting of miscarriages and stillbirths (Weigel et al., 2019).

These existing and proposed laws suggest that states could attempt to expand their reporting requirements to other entities, including clinical trial sponsors, who become aware of an induced or spontaneous abortion that occurs during the course of a clinical trial. Such information may already be provided in those states that require providers to list the reason for the abortion (e.g., in the case of a clinical trial participant, the reason may be so they can remain in the trial). States may argue that compiling this information relates to their legitimate interest in compiling vital statistics about births and deaths. Such reporting requirements are perhaps most likely to be proposed in states with fetal personhood laws, as the death of a fetus will be considered on par with the death of any person after birth.

States could justify the collection of such information by arguing that it is related to their interest in maternal health. The Supreme Court has recognized that "[r]ecordkeeping and reporting requirements that are reasonably related to the preservation of maternal health and that properly respect a patient's confidentiality and privacy are permissible" (*Danforth*, 1976).

If states were to require clinical trial sponsors to report pregnancy and abortion data about their trial participants, and if any abortions occurred in violation of state law, states could seek to hold the sponsor

civilly or criminally liable, depending on the scope and language of the state's abortion laws. As noted previously, some states provide for civil liability of those who "aid and abet" an abortion. If sponsors provide information to clinical trial participants about abortions, or even if they simply inform a participant that they must drop out of the trial if they remain pregnant, states with aiding and abetting laws could adopt a broad reading of these statutes and impose liability on trial sponsors.

In most if not all cases, the information reported to states maintains the patient's confidentiality and does not provide their name or other personally identifiable information. However, where a state has banned or severely restricted abortion, they may seek such identifiable information in pursuit of criminal charges. And even if the pregnant person is not identifiable and thus not at risk for legal consequences, the sponsor could still be subject to liability if, for example, they help participants obtain an abortion, and there is evidence that participants did in fact terminate their pregnancies. Whether any legal consequences transpire will be a matter for a court to decide. The Supreme Court has held that states have a compelling interest in pursuing criminal investigations (Branzberg, 1972). Furthermore, an individual's right to privacy is not necessarily "absolute; rather, it is a conditional right which may be infringed upon a showing of proper governmental interest" (Lawell, 2002). As described in the final section of this document, certificates of confidentiality may provide some protection against this.

The possibility of compelled reporting or disclosure of such information to a state entity may depend in part on the type of entity sponsoring the trial. In many cases, the federal government, such as the National Institutes of Health (NIH), sponsors clinical trials, raising the question of whether the state can compel a federal entity to provide it with information. This appears to be an open question in the clinical trial context. As noted above, although the primary regulatory framework for conducting clinical trials in the United States is set forth in Title 21 of the *Code of Federal Regulations*, these regulations do not preclude states from imposing their own requirements in such areas as informed consent (Administration, 2011). With respect to clinical trial registration and reporting requirements, federal law provides that "no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database" (*Food and drug administration amendments act of 2007*, 2007). Yet, even while states may not require additional *result* reporting requirements, the laws and regulations do not, however, appear to address whether or not states may request or compel information from federal government sponsors of clinical trials for purposes outside of these public reporting requirements.

Privacy concerns may make it more difficult to enroll participants. In the context of cancer research, for example, Mittal and colleagues remark that

> With the overturning of *Roe v. Wade*, women of childbearing age with a cancer diagnosis may feel discouraged and/or threatened by participating in clinical trials as therapeutic interventional studies would require documentation of regular pregnancy screening. We are concerned that the recent ruling [in *Dobbs*] will curtail the therapeutic armamentarium for oncology patients in the reproductive age group, by restricting clinical trial options for women and disempowering them from making personal health care decisions (Mittal et al., 2023).

Sugarman et al. similarly note that "If risks to research participation that result from legal restrictions on abortion access are not sufficiently addressed, people who can become pregnant might be deterred from enrolling in clinical research." This may have serious consequences, "compromise[ing] the scientific and social value of research [and reinforcing longstanding gender disparities, which are due in part to longstanding underrepresentation of people who can become pregnant in research" (Sugarman et al., 2023)

In addition to reinforcing gender disparities, ethnic and racial disparities may also be reinforced and exacerbated. Enrollment difficulties are particularly likely for participants from historically marginalized and vulnerable populations who may have less trust in government, medical, and research institutions in light of a long history of exploitation and abuse. Individuals with lower levels of trust in the health care system and researchers are less likely to participate in various kinds of research (Sanderson et al., 2017). The effects may be magnified particularly for women of color, who have experienced a long history of being unknowingly or unwilling subjected to unethical medical experiments and procedures, such as those carried out by doctors like James Marian Sims who performed myriad gynecological experiments on Black enslaved women, often without providing them any anesthesia (Whelan, 2021). Furthermore, communities of color are already susceptible to discriminatory oversurveillance and policing, including state prosecution of women for their behaviors during pregnancy (Dirks, 2022; Whelan, 2023). Communities of color are thus likely to have heightened and well-founded fears about the confidentiality of their information.

Liability

Overall, the risk of liability will likely increase post-*Dobbs* for all entities involved in research with pregnant persons. This includes the sponsor, funders, investigators/study staff, and participants. This will be particularly true in states with fetal personhood laws. As noted by

Waggoner and Lyerly (2022), "It is easy to imagine that in a legal context where fetal harm is more likely to result in criminal penalties, especially among women of color. . .the research community might conclude that a study with pregnant persons is too risky to justify—to funders, to research oversight boards, or to pregnant persons themselves."

The potential for liability depends on how far states are willing to push their antiabortion and fetal protection laws. While some states may limit their actions to research explicitly studying drugs intended to induce an abortion, others could go further, seeking to impose liability on those involved in clinical research that harms a fetus or results in fetal death. The liability could stem from a state's abortion laws, fetal personhood laws, children endangerment/abuse laws, or other criminal laws.

In the event a participant becomes pregnant but wants to remain in a trial where pregnancy is an exclusion criterion, sponsors will need to consider whether to provide participants with any information or resources about abortion. Doing so would increase their risk of being held liable for aiding and abetting an abortion.

Higher Costs

Trial sponsors may have to spend more time and resources obtaining legal advice to ensure they do not run afoul of any state's antiabortion or fetal personhood laws. They may also need to amend their informed consent documents and procedures. If sponsors encounter difficulties enrolling adequate numbers of participants, the trial may need to run longer than initially expected in order for the sponsor to collect the volume of data needed. The extra time and money may have downstream effects on the price of medication if the product makes it through trials and is ultimately approved by FDA.

Stifling Innovation

As noted in previous sections, *Dobbs* may make it more difficult to enroll pregnant persons in clinical trials and to study certain types of medical products. This may stifle innovation, both generally and specifically with respect to medications that aim to treat or prevent pregnancy-related conditions, such as gestational diabetes, preeclampsia, preterm birth, maternal–fetal disease transmission, and more.

Clinical trials for such products could be shifted to other jurisdictions in the United States or another country where abortion laws do not impose these extra hurdles. However, as noted previously, some of the states with the greatest restrictions are also the states with the highest populations of communities of color and low-income populations.

These same populations are also more likely to experience some of the diseases and conditions listed in the prior paragraph (Osuebi, 2023). As FDA acknowledges, broader and

> more-inclusive enrollment practices should improve the quality of studies by ensuring that the study population that will use the drug if the drug is approved by facilitating the discovery of important safety information about use of the investigational drug in patients who will take the drug after approval; and by increasing the ability to understand the therapy's benefit–risk profile in later stages of drug development for the Phase III population across the patient population likely to use the drug in clinical practice (Services and Administration, 2020).

Other areas of innovation that may be affected include: (1) research and development of infertility treatments and artificial reproductive technologies, particularly any that involve the creation and potential destruction of embryos;[3] (2) research involving fetal tissue and embryonic materials; (3) pre- and postimplantation gene editing; (4) research into new and potentially safer and more effective methods of medication abortion and contraception; and (5) research and development of period tracking or other fertility-related apps.

MITIGATING THE CONSEQUENCES OF *DOBBS*

This section discusses existing and new mechanisms that may help mitigate the effects of *Dobbs* on clinical research. Given that much remains unknown at this time, sponsors and other stakeholders will need to remain flexible as new or unexpected challenges arise and as laws and policies continue to evolve in the post-*Dobbs* world.

Certificates of Confidentiality

Certificates of confidentiality (CoCs) provide an important opportunity to protect against the privacy issues discussed in the previous section. The privacy and legal risks encountered post-*Dobbs* represent precisely what CoCs are intended for: to protect researchers and health care providers and research participants from unintended legal consequences.

[3] In November 2022, the Tennessee attorney general issued an opinion clarifying that disposing fertilized preimplantation embryos, such as those created in the course of IVF treatment, would not constitute a criminal abortion under the state's Human Life Protection Act, even though the Act includes preimplantation embryos in its definition of an "unborn child" (Stockard, 2022). However, it is unclear if disposal of preimplantation embryos in IVF context is the same as actively destroying an embryo in course of human embryonic stem cell (HESC) research.

The CoC is a federal statutory device that protects identifiable, sensitive information collected during "biomedical, behavioral, clinical, or other research" from compelled disclosure. Specifically, if a law enforcement officer, prosecutor, legislator, civil litigant, or other party seeks to compel information about a research participant through a subpoena or warrant, a CoC prohibits the researcher from making the disclosure and bars the use of that information as evidence. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, a CoC can help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

The statutory scheme providing for CoCs has been amended numerous times since first enacted in 1970. Every time Congress has revisited the statute, it has not only reaffirmed the importance of CoCs, but *broadened* their reach and scope. The CoC statutory scheme represents Congress's view that research is very important and should be facilitated.

The statute itself is surprisingly broad. Initially, it applied only to certain types of research. Today, that is no longer the case; the statute no longer distinguishes between different types of research, it applies to *all* types of research. In short, the law today mandates the issuance of CoCs for all federally funded research; researchers not engaged in federally funded research are eligible to apply for a CoC. As a result of this law, large volumes of research data are now covered by CoCs and therefore beyond the reach of state and federal law enforcement, legislative, and other authorities. CoCs help reassure participants that their data are safe and protected from disclosure or use in legal proceedings.

The protections offered by CoCs are broad, but not absolute. Although they protect individually identifiable research data against compelled disclosure in any "Federal, State, or local, civil, criminal, administrative, legislative, or other proceeding," they do not prevent disclosures that are "required by Federal, State, or local laws" outside of the "compelled" context. So, if a state law requires the disclosure or collection of research data for public health purposes, such as vital statistics about pregnancy outcomes, a CoC will not likely protect them from being disclosed to the state for such purposes. Importantly, however, if the information can be obtained elsewhere, the researcher can always direct the requester elsewhere.

As noted by Sugarman et al. (2023), CoCs have yet to be tested in this context in court. It is possible that antiabortion policy makers could view the post-*Dobbs* landscape as an opportunity to challenge CoCs. States may argue that such data concern public health, which has been deemed "a quintessential concern of [a state's] police power" (*Terkel v. Cdc*, 2021). States could attempt to challenge the constitutionality of CoCs, alleging that law enforcement within its borders also represents a quintessential

police power that the Tenth Amendment of the U.S. Constitution reserved to the states. Essentially, states could argue that Congress lacks the constitutional authority to statutorily disable state warrants and subpoenas that are otherwise valid.

Strong arguments can be made, however, to support the constitutionality of CoCs. These arguments would be grounded primarily in the Commerce Clause, with additional support from Congress's power to tax and spend. Using these constitutional authorities in a forthcoming law review article, Natalie Ram, Jorge L. Contreras, Laura M. Beskow, and Leslie E. Wolf, make a strong case for the constitutionality of CoCs (Ram et al., 2023).

Should the states seek the disclosure of research data under one of the legitimate exceptions to a CoC's protections, one might be concerned that the state could then later use that information in a legal proceeding, even if they originally used it for a valid purpose. In this situation, there is a strong argument that the information should be inadmissible. The statute was amended under the 21st Century Cures Act to apply to *all* copies in perpetuity. Therefore, a copy of the information initially obtained for a valid reason could not later be used for an invalid reason (e.g., in a legal proceeding).

One potential and important loophole in the context of clinical trials involving pregnant persons and CoCs is mandatory reporting laws. A CoC protects research subjects from legally *compelled* disclosure of their identity and sensitive information. It does not, however, restrict voluntary disclosure. For example, a CoC does not prevent researchers from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or reporting a communicable disease. If researchers intend to make such disclosures, that should be clearly stated in the consent forms that research participants are required to sign. Child abuse reporting laws could come into play in states with fetal personhood laws or that criminalize certain behaviors of pregnant persons, classifying things like drug or alcohol use as child abuse. But importantly, these disclosures are *voluntary*—researchers are not *required* to report them.

In sum, despite some limitations, CoCs appear to provide a very strong mechanism currently available to protect against the many concerns addressed in the previous section.

Congressional Action

Congress has historically shown support for research involving human subjects. Congress illustrates its support in various ways, such as through the passage of laws, the establishment of agencies that govern or conduct biomedical research, and the provision of significant funds

to support biomedical research. NIH, for example, invests most of its multibillion dollar annual budget in medical research (Health, 2022). Recent congressional support for research is shown by the creation of the Advanced Research Projects Agency for Health (ARPA-H), which was established in March 2022 to support the development of high-impact research to drive biomedical and health breakthroughs to deliver transformative, sustainable, and equitable health solutions (*Consolidated Appropriations Act, 2022*, 2022).

Executive agencies also play a role in protecting health privacy, and recent actions by HHS illustrate concerns about the privacy of reproductive health information. HHS has issued a notice of proposed rulemaking that would modify the Standards for Privacy of Individually Identifiable Health Information (i.e., the "Privacy Rule") under HIPAA and the HITECH Act. The proposed rule would modify existing standards permitting uses and disclosures of PHI for certain purposes where the use or disclosure of information is about reproductive health care that is lawful under the circumstances in which such health care is provided. The proposal would modify existing standards by prohibiting uses and disclosures of PHI for criminal, civil, or administrative investigations or proceedings against individuals, covered entities or their business associates (collectively, "regulated entities"), or other persons for seeking, obtaining, providing, or facilitating reproductive health care that is lawful under the circumstances in which it is provided.

An important limitation of the proposed rule is that it only prevents the use and disclosure of PHI that relates to reproductive health care that is *lawful under the circumstances in which such health care is provided*. So if a state seeks the information because they believe an abortion was performed or a fetus was harmed in violation of a state law, the proposed rule would not protect that information from disclosure. Under this rule, a CoC, as described above, would still be needed to protect the information from disclosures made for purposes of various types of legal proceedings.

Institutional Review Boards (IRBs)

IRBs should consider specifically reviewing *Dobbs*-related risks, such as risks related to restrictions on abortion access to participants who may become pregnant. IRBs should also consider ways to minimize any such risks. To perform their oversight responsibilities, IRB members will need to understand and have a working knowledge of relevant state law that will apply to the trial protocol, and they should consult with those with appropriate expertise when necessary.

IRBs should consider, for example, whether *Dobbs*, or any new state laws that have been enacted in the wake of *Dobbs*, make it illegal or extremely risky to conduct certain studies in certain states. Informed consent procedures should also be reviewed with an eye toward *Dobbs*. These may be complicated and time-consuming obligations, given the variability and evolving nature of laws across the states, but they remain necessary.

According to William Alford at Public Responsibility in Medicine and Research (PRIM&R), a nonprofit organization that provides education, membership, and other professional resources to the research and research oversight community, the organization has not provided any information to IRBs about abortion/*Dobbs*-related factors (e.g., legality of abortion) when assessing whether to approve certain studies.

Sponsors and other stakeholders should consider whether all research with the potential to affect a pregnancy should be governed by IRBs comprised of members with adequate expertise to determine the myriad risks associated with new state laws, including privacy risks. Currently, IRB approval for research involving deidentified data is not required unless the researcher has access to a link allowing reidentification (Services, 2017). However, evolutions in technology make it increasingly easy to reidentify deidentified information, so it would be wise for sponsors to engage an IRB or other privacy experts to ensure their data are protected adequately.

Compensation and Reimbursements for Participants

Sponsors of clinical trials often reimburse patients for costs related to their participation in research (e.g., travel). Given the increasing number of states enacting abortion bans and restrictions that may make it difficult to conduct certain types of clinical research in that state, sponsors will need to consider whether they have the resources to reimburse participants for longer-distance travel, hotel stays, and overnight stays. This approach may help mitigate the effect of *Dobbs* on clinical trial diversity discussed in the previous section. Yet even if these costs are reimbursed, requiring persons to uproot their lives and essentially move temporarily during the duration of the trial still represents a substantial burden that would be likely to discourage enrollment. There is also a sustainability issue—will sponsors be able to sustain such levels of reimbursement in the long term?

As always, sponsors will need to keep abreast of state laws that attempt to criminalize abortion-related travel. Sponsors must also ensure that any reimbursement or compensation provided to participants do not cross a line so as to become coercive (Largent et al., 2012).

Liability Insurance

Sponsors should work closely with insurers to develop insurance policies that provide broad liability and/or indemnity coverage. An important limitation here is that many abortion laws now impose criminal penalties, which are likely beyond the scope of any protection from insurance policies.

Lawsuits

If a state law attempts to collect confidential information from trial sponsors or other parties, a lawsuit could challenge the law on the grounds that the state does not have legitimate need or reason for collecting such information. Trial sponsors, investigators, health care providers involved in the participant's care, and/or the participants might, for example, challenge the constitutionality of these laws, specifically as they relate to the constitutional right to privacy.

States may, however, have relatively strong arguments in support of their laws, even if the laws include the collection of identifiable information. States will argue that these laws are a valid and reasonable exercise of their broad police powers. The Supreme Court has long recognized the breadth of the states' police powers, which provide states with broad authority "to establish and enforce standards of conduct within [their] borders relative to the health of everyone there" (*Barsky*, 1954). Back in 1909, for example, in *District of columbia v. Brooke*, 1909, the Court stated that the "exercise of the police power" represents "one of the least limitable powers of the powers of government." The Court's recognition of strong state police powers may make it difficult to overcome the state's argument in these cases.

These lawsuits might make similar claims to those made by the petitioners in *Whalen v. Roe* (1977), a 1977 Supreme Court case that challenged New York statutes that classified potentially harmful drugs and provided that the prescriptions for Schedule II drugs (the most dangerous legitimate drugs) be prepared on an official form. One copy of the form, which identified the prescribing physician, dispensing pharmacy, drug and dosage, and the patients name, address, and age, was required to be filed with the State Health Department, where data were recorded on tapes for computer processing. All forms were retained for a 5-year period and thereafter destroyed. Public disclosure of the patient's identity was prohibited and access to the files was confined to a limited number of state personnel. Prescribing physicians and a group of patients regularly prescribed these drugs challenged the constitutionality of the Schedule II patient-identification requirements. The Supreme Court, however, upheld

the laws, concluding: (1) the patient identification requirement was a reasonable exercise of the State's broad police powers; (2) neither the immediate nor threatened impact of the patient identification requirement on either the reputation or independent of patients sufficed to constitution an investigation of any right or liberty protected by the Fourteenth Amendment; and (3) there was no merit to the prescribing doctors' contention that the law impaired their right to practice medicine free from unwarranted state interference.

In the case of clinical trial information about pregnancy outcomes, the state could reasonably claim an interest in protecting maternal and fetal health. And now that *Roe* has been overturned, there is no countervailing constitutional right to abortion to counteract that state interest. A state also has an interest in maintaining a vast array of vital statistics, including data on pregnancy outcomes, maternal health, and fetal health. Moreover, in the case of clinical trial data, courts may not view pregnancy-related information from clinical trial sponsors as implicating the physician–patient relationship, so those interests may not even come into play as a countervailing interest to the state's interest. Courts generally have not recognized researchers as having a researcher–participant privilege, which might offer similar protection as the doctor–patient privilege.

CONCLUSION

This report described how the U.S. Supreme Court's decision in *Dobbs v. Jackson Women's Health Organization* may affect clinical research involving pregnant and lactating persons. On the one hand, this report concludes that *Dobbs*, and the state laws and regulations that have transpired or may transpire from that decision, is unlikely to have a significant effect on research involving lactating persons. On the other hand, they are likely to make research involving pregnant persons more difficult, costly, and rife with legal uncertainties and risks.

All stakeholders involved in clinical research must remain abreast of the evolving legal landscape. This report has described some potential considerations and mitigation strategies for sponsors. The most important tool currently at the disposal of trial sponsors is certificates of confidentiality, which should be used and defended rigorously. Importantly, sponsors must remain vigilant and flexible as the reproductive health care landscape continues to change.

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