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Scientific, ethical, and legal considerations for the inclusion of pregnant people in clinical trials

Catherine A. Sewell, MD, MPH; Sarah M. Sheehan, MPA; Mira S. Gill, BA; Leslie Meltzer Henry, JD, PhD; Christina Bucci-Rechtweg, MD; Cynthia Gyamfi-Bannerman, MD, MSc; Anne D. Lyerly, MD; Leslie C. McKinney, PhD; Kimberly P. Hatfield, PhD; Gerri R. Baer, MD; Leyla Sahin, MD; Christine P. Nguyen, MD

Clinical trials to address the COVID-19 public health emergency have broadly excluded pregnant people from participation, illustrating a long-standing trend of clinical trial exclusion that has led to a clear knowledge gap and unmet need in the treatment and prevention of medical conditions experienced during pregnancy and of pregnancy-related conditions. Drugs (includes products such as drugs, biologics, biosimilars and vaccines) approved for a certain medical condition in adults are also approved for use in pregnant adults with the same medical condition, unless contraindicated for use in pregnancy. However, there are limited pregnancy-specific data on risks and benefits of drugs in pregnant people, despite their approval for all adults. The United States Food and Drug Administration—approved medical products are used widely by pregnant people, 90% of whom take at least 1 medication during the course of their pregnancy despite there being sparse data from clinical trials on these products in pregnancy. This overall lack of clinical data precludes informed decision-making, causing clinicians and pregnant patients to have to decide whether to pursue treatment without an adequate understanding of potential effects. Although some United States Food and Drug Administration initiatives and other federal efforts have helped to promote the inclusion of pregnant people in clinical research, broader collaboration and reforms are needed to address challenges related to the design and conduct of trials that enroll pregnant people, and to forge a culture of widespread inclusion of pregnant people in clinical research. This article summarizes the scientific, ethical, and legal considerations governing research conducted during pregnancy, as discussed during a recent subject matter expert convening held by the Duke-Margolis Center for Health Policy and the United States Food and Drug Administration on this topic. This article also recommends strategies for overcoming impediments to inclusion and trial conduct.

Key words: clinical trials, clinical trial conduct, fetal health, maternal health, research during pregnancy, US Food and Drug Administration

Introduction

The COVID-19 pandemic has underscored the ethical and health care delivery implications of the failure to enroll pregnant people in clinical trials, and has accentuated the already evident need for efficacy and safety data to inform the use of critical medical products during pregnancy.[1] The data necessary to support the emergency use authorization of COVID-19 prevention and treatment measures for the adult population were accrued with unprecedented speed, outpacing the availability of clinical data to support timely enrollment of pregnant people in trials, and leading to conflicting recommendations about COVID-19 vaccine use in pregnancy.[2,3] Despite early studies indicating that pregnant people are at higher risk of developing complications owing to COVID-19, and despite recommendations from the US Food and Drug Administration (FDA) COVID-19 guidance[4,5] and other organizations and experts for the inclusion of pregnant

From the Division of Urology, Obstetrics and Gynecology, United States Food and Drug Administration, Silver Spring, MD (Dr Sewell); Duke-Margolis Center for Health Policy, Washington, DC (Mses Sheehan and Gill); University of Maryland Carey School of Law and Johns Hopkins Berman Institute of Bioethics, Baltimore, MD (Dr Henry); Novartis Pharmaceuticals Corporation, East Hanover, NJ (Dr Bucci-Rechtweg); Department of Obstetrics, Gynecology & Reproductive Sciences, University of California San Diego School of Medicine, San Diego, CA (Dr Gyamfi-Bannerman); Department of Social Medicine and Center for Bioethics, University of North Carolina at Chapel Hill, Chapel Hill, NC (Dr Lyerly); Division of Pharmacology Toxicology for Rare Diseases, Pediatrics, Urology and Reproductive Medicine, United States Food and Drug Administration, Silver Spring, MD (Drs McKinney and Hatfield); Office of Pediatric Therapeutics, United States Food and Drug Administration, Silver Spring, MD (Dr Baer); Division of Pediatric and Maternal Health, United States Food and Drug Administration, Silver Spring, MD (Dr Sahin); and Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine, United States Food and Drug Administration, Silver Spring, MD (Dr Nguyen).

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Corresponding author: Catherine A. Sewell, MD, MPH. catherine.sewell@fda.hhs.gov

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people in clinical trials, COVID-19 medical product development did not specifically focus on the particular condition of pregnancy. The exclusion of pregnant people in COVID-19 trials is one example of their routine exclusion from medical product trials more broadly. In addition, there is little clinical development of products for pregnancy-related conditions. As a consequence of these practices, both patients and their providers often have sparse information, if any, with which to assess the benefits and risks associated with medical product use during pregnancy for both the pregnant person and the developing fetus. Limited or absent information can lead to unsafe use of medical products or refusal or reluctance to prescribe or accept necessary treatment.

The COVID-19 medical product trials illustrate a long-standing trend of excluding pregnant people from clinical trials for prescription and nonprescription drug products and biologic products (including vaccines), which has led to a clear knowledge gap and unmet need for evidence to inform both pregnancy-related conditions and medical conditions existing in pregnancy. Approximately 90% of pregnant people take at least 1 medication in pregnancy, and 70% of those who are pregnant take at least 1 prescription medication.[6–8] Medical products that are approved for adults are also approved for pregnant populations because pregnant people are adults, barring a contraindication for the use of some products during pregnancy, even if pregnancy-specific data are lacking. Dosing studies of medical products for conditions that exist in pregnancy often do not include pregnant people, forcing clinicians to use their clinical judgment to extrapolate appropriate dosage for similar efficacy when prescribing treatments in pregnancy, potentially leading to ineffective treatment or excess toxicity. This knowledge gap, and the potential adverse impact on patient care, underscores the importance of planning for the collection of data needed to support use in pregnancy at the beginning of product development programs. To address the knowledge gap, it is critical that studies necessary to support enrolling pregnant people in clinical trials, including nonclinical developmental and reproductive toxicity studies and clinical pharmacology studies, are conducted as early as possible.

The overall lack of clinical data in pregnancy presents important challenges that regulators and clinicians are actively seeking to address. To guide and manage the use of medical products in pregnant populations, regulatory decision-makers and clinicians must often rely on safety data from nonclinical studies and efficacy and safety studies in the nonpregnant population. Even if data in pregnant people are eventually collected in the postapproval setting, this accrual often occurs slowly; hence, the evidence gap persists for an extended period of time after product approval. Furthermore, data collected in the postapproval setting in pregnant people are often subjected to inherent biases and confounders that may not be adequately mitigated.

To address this knowledge gap and encourage timely evidence generation for pregnant populations, federal agencies, patient organizations, and collaborative public–private partnerships have actively raised awareness of key issues and are taking steps to boost inclusion of pregnant people in clinical trials (Table).

Although these initiatives have helped promote the inclusion of pregnant people in clinical research, broader collaboration and reforms are needed to address challenges related to the design and conduct of trials that enroll pregnant people and to forge a culture of widespread inclusion of pregnant people in research.

Accordingly, the Duke-Margolis Center for Health Policy, under a cooperative agreement with the FDA, convened a public meeting in February 2021 to discuss the scientific and ethical considerations for including pregnant people in clinical trials. Meeting participants represented a wide variety of stakeholder categories including academia, industry, governmental agencies, and patient advocacy groups. Below, we summarize key input from meeting participants about the scientific, ethical, and legal considerations governing research for pregnancy, and provide their recommendations on approaches to overcome impediments to including and conducting trials in pregnant people.

Scientific considerations

Nonclinical and clinical data are essential components of drug development, and both are critical for regulatory and clinical decision-making for all patient populations. The scientific considerations and associated challenges discussed during the meeting fall into the following categories:

1. Nonclinical studies to support the conduct of clinical trials in pregnant people
2. Clinical data collection to support regulatory decision-making and evidence-based care delivery

Nonclinical studies to support trial conduct

Nonclinical studies provide key safety information that informs clinical trial eligibility criteria, dosing decisions, and drug labeling. Generally, nonclinical studies to support enrolling pregnant people in clinical trials include nonclinical safety assessments from reproductive and developmental toxicity studies in animals. At the meeting, representatives from the FDA described the characteristics of standard nonclinical studies and their utility and limitations. Detailed information regarding general and specific nonclinical study conduct and design can be found in a multitude of published guidances by FDA, and in conjunction with worldwide regulatory agencies through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Two pertinent resources for this topic are ICH M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, and ICH S5 (R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.[9,10]

TABLE
Federal efforts to advance therapeutic research in pregnancy

FDA initiatives		
FDA Office of Women's Health[18]: • Advises the FDA Commissioner on topics related to women's health • Provides funding for research related to women's health • Maintains a pregnancy registry webpage, supports workshops, and develops educational resources for pregnant people	FDA Perinatal Health Center of Excellence[19]: • Collaborates with other FDA centers and external organizations to support research to advance regulatory science for perinatal populations	FDA draft guidance: • Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials • Postapproval Pregnancy Safety Studies
National Institutes of Health initiatives		
PregSource[20]: • Collects information from pregnant people about pregnancy and overall maternal health	Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub[21]: • Collects tools and data to further maternal and pediatric therapeutic development	Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES)[22]: • Developing guidance for conduct of clinical trials for HIV in pregnancy
PRGLAC		
PRGLAC Report to the HHS Secretary and Congress, September 2018[7]: • Describes knowledge gaps and ethical considerations related to research in pregnant and lactating people • Includes the Task Force's 15 recommendations to improve therapeutic development for pregnant and lactating people	PRGLAC Report Implementation Plan to HHS Secretary, August 2020[23]: • Outlines implementation plan for the Task Force's 15 recommendations	

FDA, Food and Drug Administration; *HHS*, United States Department of Health and Human Services; *PRGLAC*, Task Force on Research Specific to Pregnant Women and Lactating Women.

Sewell. Inclusion of pregnant people in clinical trials. Am J Obstet Gynecol 2022.

Meeting participants primarily discussed the characteristics and requirements of 2 types of nonclinical studies: reproductive toxicity and developmental toxicity studies. Reproductive toxicity studies assess how drugs may affect the reproductive competence of sexually mature males and females. Developmental toxicity studies assess possible adverse effects from drug exposure from preconception, prenatal, or postnatal exposure on the developing fetus up to sexual maturity. These nonclinical studies use animal models (typically rats and rabbits) that allow safety assessment across gestational stages, can be completed efficiently, and are intended to inform safe use of medical products throughout pregnancy. These nonclinical animal models are well established and accepted worldwide for drug registration, have significant background control data, have targeted treatment periods with specific endpoints, and are intended to interrogate high doses of drug molecules.

In general, pregnancy-related information in the drug label to inform prescribing decisions in the pregnant person consists solely of evidence from nonclinical studies at the time of drug approval. Although nonclinical studies provide essential information, they also have limitations. First, although rats and rabbits serve as effective animal models, the inherent species differences between these animals and humans can lead to some uncertainties when extrapolating from animals to humans. For example, some studies in animals may produce safety signals at high doses that would not appear in humans because of species and related dosage differences, and thus may provide some assurance for human safety. Conversely, animal studies may not capture harms that may occur in human pregnancies. In addition, there are study design limitations that affect the translational utility of available animal models. For example, nonclinical reproductive and developmental studies are designed to capture only gross morphologic and easily observable functional effects of a drug. Thus, standard study designs do not include assessments of drug effects on higher-order learning and memory, immune system development, endocrine system functioning following puberty, or animal fetal exposure levels; although specially designed studies can capture these data if there is a known concern that warrants these special studies.

Although nonclinical studies have limitations, they are a vital component to informing clinical research in pregnant populations and must be completed before progression to later stages of clinical trials that enroll pregnant people. Thus, the timing of reproductive and developmental studies in the drug development program is critical when planning for trials enrolling pregnant people. Although it would seem ideal to perform these nonclinical studies early to inform risk, doing so before knowing the doses to be investigated in a nonpregnant population in a clinical

trial can increase overall cost, prolong data collection timelines for the general drug development program, and may delay therapeutic availability to the general population. For most drugs intended for the general population, fertility and early embryonic development (FEED) and embryofetal development (EFD) studies are not conducted until after or concurrently with Phase 2 studies, whereas pre- and postnatal development (PPND) studies are often concurrent or prior to Phase 3. For drugs expected to be used by people who may need treatment in pregnancy, conducting these nonclinical studies early in drug development to specifically identify any pregnancy-related risks would allow earlier inclusion of pregnant people in clinical trials and facilitate the timely collection of pregnancy-specific human data before product approval.

Clinical data collection for decision-making

Physiological considerations

Clinical research during pregnancy is critical for supporting safe and effective drug use because physiological changes during pregnancy can affect the pharmacokinetics (PK) of a drug and thus the dosage needed to reach the intended therapeutic effect compared with nonpregnant populations. Such physiological changes include: doubling of blood volume, fluctuations in levels of circulating binding proteins, slower gastrointestinal transit time, and alterations in metabolism and excretion. Each of these changes can vary over the duration of the pregnancy, thus it is important to study therapeutic effect and dosing throughout gestation.

Numerous patient characteristics and medical conditions may coexist with pregnancy, such as diabetes mellitus, hypertension, chronic kidney disease, and liver disease that can affect drug metabolism, further underscoring the need for robust PK studies in pregnant people to guide safe and effective dosing. In addition, fetal and placental development can affect disposition of therapeutics during pregnancy because different gestational stages are associated with different susceptibilities and fetal and placental physiological changes.

Absent knowledge of PK in pregnancy, the appropriate modifications in dosing to match physiological changes are unknown and may result in either underdosing and inadequate treatment, or overdosing leading to toxicities.

Trial design considerations

Clinical research considerations also include those related to trial design and conduct. Clinical trial design and conduct are influenced by factors such as the drug class, study objectives, disease area, and therapeutic context. Therapeutic context depends on various factors including the nature of the disease, whether there is an unmet medical need, availability of treatments, and the potential benefits and risks of a medical product.

The objectives of clinical trials during pregnancy can be divided into 2 broad categories:

1. To support the development of therapeutics for pregnancy-related conditions (eg, preterm birth, preeclampsia, intrahepatic cholestasis of pregnancy)
2. To support the development of therapeutics for medical conditions that coexist with pregnancy (eg, hypertension, diabetes mellitus, COVID-19)

In addition to clinical trial design, there was extensive discussion at the meeting about trial conduct and clinical data collection considerations to allow timely accrual of evidence for the use of medical products in pregnancy. For example, participants discussed a proposed framework for conducting clinical trials in pregnant people earlier in drug development. Participants emphasized that it was both possible and preferable to begin evaluation in pregnant people during Phase 3 or earlier, as opposed to conducting it solely in the postapproval setting, with appropriate consideration given to therapeutic context.

Participants noted there were major operational barriers to pursuing some of these approaches in both private- and public-sector research. These barriers are discussed in the legal considerations section.

Ethical considerations

Meeting participants from all stakeholder categories agreed that reticence to include pregnant people in trials prevents collection of data that inform assessments of safety, efficacy, and therapeutic dosage, thereby precluding adequate information for informed decision-making in pregnancy. However, several participants noted that barriers to enrolling pregnant people in clinical trials persist largely because of ethical concerns and outdated or misinformed ideas about clinical research.

A meeting participant specializing in bioethics stated that clinical research in pregnant people has been guided by a protectionist ethic, which has ultimately had harmful consequences. The protectionist ethic has limited the autonomy of pregnant persons, led to their exclusion from research, and exposed them and their children to harms of constrained evidence. The protectionist ethic manifests, for example, in a regulation guiding clinical trials in pregnancy that requires paternal consent, in addition to maternal consent, when the prospect of direct benefit applies only to the fetus. This requirement fails to acknowledge that the interests of a pregnant person and their fetus are intertwined strands in contrast to research conducted in pediatric settings, where the consent of one parent is sufficient to authorize research with a prospect of direct benefit to a child. In addition, participants underscored the importance of considering altruism given that pregnant people may choose to participate in research not only when there is a direct benefit to study participants but also when the research could benefit other current and future pregnant people.

Furthermore, researchers discussed the ethical implications of requiring contraception in certain trials where it would not be needed or medically acceptable to do so. Participants highlighted that requiring contraception in cases where there is no prospect of pregnancy (eg, a trial participant in a

same-sex relationship) raises ethical concerns by imposing unnecessary requirements or preventing participation in a study.

Ultimately, the meeting participant emphasized the ethical principle of protecting pregnant people, not from research, but through research. In preventing research in pregnant people, the protectionist ethic does not in fact eliminate or mitigate potential harm from medical products. Rather, the potential for harm remains unknown in a clinical setting where prescribers and patients must make decisions about treatment, potentially exposing a larger number of individuals to adverse events than would occur in a trial setting. Including pregnant people in clinical trials provides the opportunity to assess potential risks in a controlled setting, so that risk mitigation strategies can be identified to inform clinical care.[11] Finally, efforts to "protect" pregnant people from research, which inevitably lead to insufficient data, have led to the reluctance to prescribe or accept necessary treatment, putting pregnant people in harm's way from absent or undertreatment.

Another meeting participant specializing in bioethics discussed 2 overarching ethical questions associated with trial conduct and developing an ethical framework. The first question was: "When is it ethically permissible to allow enrollment of pregnant people into clinical research?" Participants noted that researchers should first assess whether there is preliminary evidence during a drug development program indicating potential safety signals. In addition, researchers should decide whether the development program involves acceptable research-related risk. This includes assessing the benefit−risk ratio rather than just the potential risk. Thus, it generally follows that the more potential benefit offered through participation in a given trial, the greater the risk that might be acceptable to the research participant.

The second question highlighted was: "When do we have an ethical responsibility to enroll pregnant people in a trial (eg, if it is permissible to enroll, do we have a responsibility to enroll)?" Participants noted that researchers should consider the degree to which obtaining adequate evidence for the use of medication in pregnancy, or access to prospect of benefit from trial participation raises concerns of justice, and if so, whether exclusion of pregnant people is appropriate.

Meeting participants emphasized that the ethical framework governing enrolling pregnant people in clinical trials should be based on protecting pregnant people through inclusion in research. For example, participants noted that institutional review boards (IRBs), funders, and other stakeholders can elevate the ethical responsibility to include pregnant people in research by requesting justification for their exclusion when pregnant people are excluded from research. The development of a framework or common criteria considered adequate justification for exclusion could facilitate such efforts.

Legal considerations

In addition to ethical considerations, participants discussed how legal considerations, such as perceptions of liability, dissuade industry sponsors and research institutions from enrolling pregnant people in clinical trials. One legal expert highlighted 4 key legal considerations that influence stakeholder decision-making about whether to include pregnant people in clinical trials.

First, the participant noted, there is a myth that including pregnant people in research is legally impermissible. Although FDA guidance and federal regulations set forth criteria for ethically and legally conducting such research,[12,13] some members of the research enterprise mistakenly believe that the law precludes research during pregnancy.[14] That misperception of the law can lead to decisions—by industry sponsors, academic institutions, clinical investigators, and others along the research pathway—that exclude pregnant people from research.[15]

Second, this myth is amplified by a combination of absent and ambiguous regulations. Current federal regulations governing research during pregnancy (commonly referred to as "Subpart B"[16]) neither require the inclusion, nor penalize the unjustified exclusion, of pregnant people in research. In addition, Subpart B contains ambiguities, such as the concept of "minimal risk," that are open to wide interpretation. In the face of regulatory ambiguity, and without a clear directive to include pregnant people in research, stakeholders can apply conservative regulatory interpretations that limit the inclusion of pregnant people in clinical trials.

Third, inclusion of pregnant people in a clinical trial may increase trial and overhead expenses (eg, expenses related to liability coverage). Inclusion may also lead to slower trial recruitment if a minimum sample of pregnant people is required, leading to delays in trial completion and drug approval. Exclusion, by contrast, not only allows researchers to avoid those costs and delays, but also mitigates risks for industry by eliminating premarket liability and shifting postmarket liability to prescribers and patients, who ultimately decide whether to use medications without pregnancy-specific data.

Fourth, although liability is frequently cited as a reason that decision makers exclude pregnant people from research, the legal expert highlighted that most stakeholders' fears of liability for harms to pregnant subjects and their fetuses and offspring exceed evidence of actual liability. Although premarket testing is not risk-free, liability is limited to the size of the research population and may be mitigated by obtaining fully informed consent from each participant in research. By contrast, legal risk might increase substantially after a drug enters the market if, for example, adverse events occur in a patient population that was excluded from clinical research.

Finally, the legal expert and other panelists highlighted several key legal strategies to advance inclusion of pregnant people in clinical trials. First, it is imperative to determine the degree of, and mitigate, liability stemming from premarket clinical trials. Risk mitigation strategies, such as implementing

programs that provide compensation for research-related injuries, can dampen disincentives to including pregnant people in research.[17] Second, incentivizing research during pregnancy will also promote inclusion of pregnant people in clinical trials. For example, public funding opportunities or accelerated drug review could serve to incentivize clinical research in pregnant populations. All participants agreed that concrete liability reforms and targeted educational initiatives are necessary for encouraging clinical research in pregnant people. Furthermore, to accomplish the goals listed above, clinical research in pregnancy must be seen as a critical public health issue, and legal experts, from both within and outside of the research enterprise, should be engaged to develop workable strategies.

Next steps

To ensure appropriate enrollment of pregnant people in clinical trials, and address evidence gaps that stem from lack of enrollment, there must be a shift toward creating a culture of inclusion of pregnant people in clinical trials rather than routinely excluding them without adequate justification. As mentioned above, the clinical research community can aid in cultivating this, in part, by framing the evidence gap as a critical public health concern. Doing so would raise awareness for this crucial issue and illustrate the need for collaboration among various stakeholders to affect widespread change.

In the absence of legislative authorities for FDA, the research community and government stakeholders can also begin holding investigators accountable for including pregnant people in research by encouraging inclusion or requesting a justification for their exclusion before a trial receives IRB authorization. Support for these measures is building. These steps can be taken without new regulations and guidelines because the existing regulatory oversight infrastructure is sufficient to support inclusion of pregnant people in clinical research.

Although creating a culture of inclusion will take time, stakeholders can take steps now to identify and address priority evidence gaps and prioritize resources on the basis of unmet need. For example, researchers can begin by studying medications that are already being used in pregnant people but for which there are no objective data derived from clinical research to support the medication use in pregnant people. In addition, the clinical research community can encourage stakeholders to develop criteria (eg, frequency of use, seriousness of unmet medical need) for identifying priority medications for study in pregnancy and devote resources accordingly. Researchers can leverage existing data and trial infrastructure to obtain evidence to facilitate regulatory and clinical decision-making for drugs already being used by pregnant people in the postmarket setting.

Meeting participants from industry, federal agencies, and academic research institutions alike described how existing data such as electronic health records and registry data could be leveraged to support evidence generation. In addition, data collection through trial networks that have access to more clinical sites and patients could support increased enrollment and maximize data utility, whereas alternative data sources can be used to supplement clinical data collection for regulatory submissions and clinical decision-making.

Finally, increased collaboration among stakeholders (federal agencies, industry, academia, and patients and patient advocates) involved in each phase of drug development can support progress in a variety of ways. First, stakeholder cooperation can encourage liability reform and education. Second, increasing collaboration can aid in the implementation of innovative trial approaches, such as the development of master protocols, to reduce time- and cost-related burdens and encourage earlier enrollment of pregnant people in drug development. Third, increasing collaboration and communication with the FDA to support timely collection of nonclinical data and discuss study design can facilitate earlier enrollment of pregnant people in clinical trials. Finally, increasing both public and private funding to support nonclinical and clinical data collection can further incentivize and support clinical research in pregnancy. ■

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