

Scientific and Ethical Considerations for the Inclusion of Pregnant Women in Clinical Trials

Virtual Meeting • Zoom
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Discussion Guide

Introduction

Approximately 90% of people who are pregnant take at least one medication during the course of pregnancy, and 70% of those who are pregnant take at least one prescription medication.^{1,2,3} However, pregnant people have historically been excluded from clinical trials of new and existing medications.¹ Although drugs approved for certain conditions in adults by the United States Food and Drug Administration (FDA) are approved for all adults, including pregnant people with those conditions (unless otherwise specified), data on safety and dosing in pregnancy are largely unavailable.² Clinical decision-making is often challenging when there are sparse data to inform safe and appropriate dosing for people who require treatment during pregnancy. This could result in numerous adverse consequences, including inappropriate dosing, patient avoidance of needed therapy, and prescriber's reluctance to prescribe.^{1,4,5} Furthermore, many pregnancy-related conditions do not have any approved pharmacologic treatments. The benefits of including pregnant people in research and the disadvantages of excluding these people, even if seemingly for their own protection, are apparent.

Recognizing this gap, the 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to identify and address areas for research on safe and effective therapies for pregnant and lactating people.⁶ Federal regulations regarding trials conducted or supported by the Department of Health and Human Services (HHS) lay out additional requirements for research conducted during pregnancy, such as the requirement to conduct certain nonclinical studies, which include studies on pregnant animals, during drug development.⁷ While not all studies submitted to the FDA are necessarily subject to these HHS regulations, the FDA has developed draft guidance which recommends that trials adhere to the HHS regulations to support research conducted during pregnancy.⁸

Although the need for clinical trials to inform efficacy, safety, or dosing in pregnancy is clear, there exist a number of barriers to such trials. For example, the funding of pharmacokinetic research in pregnancy is provided primarily by governmental bodies; one study reported that the pharmaceutical industry was the funder for only 8.8% of pharmacokinetic studies in pregnant people.⁹ Compared to pharmaceutical industry investigators, academic or clinician investigators may be less aware of the requirements for appropriate nonclinical studies that could support clinical research in pregnant people. Similarly, academic or clinician investigators may have fewer resources for acquiring such data compared to investigators from large pharmaceutical industry organizations. Finally, the liability concerns of industry sponsors and academic and clinician investigators may account for the hesitancy in funding and conducting clinical research in pregnant people.

Increasing understanding of the requirements associated with the conduct of clinical trials in pregnancy and removing barriers through changes to the paradigms and infrastructure supporting clinical trial design and conduct may help facilitate this important research. To this end, the Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with FDA, is convening this public meeting to discuss the need for clinical research in this complex population, as well as the

scientific and ethical considerations for the inclusion of pregnant people in clinical trials. This workshop will explore topics including:

- Regulatory, scientific, and ethical considerations for the enrollment of pregnant people in clinical research, as articulated in existing FDA Guidance;
- Priority areas of unmet need for clinical data collection and therapeutic development in obstetrics;
- Clinical trial designs for studies enrolling pregnant people, to evaluate the dosing, safety, and efficacy of therapeutics for chronic or acute medical conditions that require treatment during pregnancy as well as for pregnancy-related conditions; and,
- Characteristics of a standard nonclinical program designed to assess the safety of a product to be used during pregnancy.

Session 1: Understanding the Need and Existing Guidance for the Participation of Pregnant People in Clinical Trials

There are numerous situations where acquiring important biomedical knowledge requires research in pregnant individuals. The development of therapies for pregnancy-related conditions (e.g., gestational diabetes, pre-eclampsia, hyperemesis gravidarum, preterm labor) must involve the enrollment of pregnant people in clinical trials. Similarly, obtaining appropriate dosing and safety information for therapies approved for general medical conditions in adults that are used commonly in pregnancy necessitates the collection of clinical data in pregnant people. This data collection is particularly important because the physiologic changes that occur throughout pregnancy (including increased blood volume and metabolic changes) can affect the pharmacokinetics and pharmacodynamics, and thus the safety and potentially efficacy, of drugs.⁴ Research in pregnancy is also necessary to understand the propensity of medications to cross the placenta and impact the fetus through various stages of development.^{4,10}

Research involving pregnant people is subject to various federal regulations. Clinical trials regulated by FDA must abide by 21 CFR part 50, “Protection of Human Subjects” and 21 CFR part 56, “Institutional Review Boards”.^{11,12} Research involving pregnant people supported or conducted by HHS must abide by 45 CFR 46, subpart B, “Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,” which lays out a series of conditions which must be met for pregnant people to participate in a research study.^{7,12} Though FDA human subject protection regulations and 45 CFR 46 are generally the same, FDA human subjects protection regulations do not contain analogous requirements found in 45 CFR 46, subpart B (Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research).

Well-designed clinical trials can support the generation of safety, dosing, and efficacy data for therapies in pregnant patients, inform prescribing practices, and reduce the risk of morbidity and mortality in both pregnant people and fetuses. The 2018 FDA Draft Guidance, *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*, outlines recommendations for when and how best to include pregnant people in trials.⁸ Various federal agencies have undertaken efforts to support quality in the design and conduct of trials enrolling pregnant people, including the 2010 workshop, Clinical Research Enrolling Pregnant Women, convened by the National Institutes of Health’s Office of Research on Women’s Health.¹³ Most recently, in 2016, the 21st Century Cures Act established the PRGLAC Task Force to report to the Secretary of HHS on gaps in scientific knowledge and research surrounding medical therapies for pregnant and lactating people.⁶ The PRGLAC Task Force issued a report to the Secretary in 2018, with fifteen recommendations.² Its mandate was subsequently extended two

additional years to develop plans to implement the recommendations. The task force subsequently released a [report implementation plan](#) in August 2020.¹⁴

Session presenters will speak about the need for enrolling pregnant people in clinical research. This session will also outline FDA's guidance and regulations governing this research and cover the recommendations and the implementation plan of the PRGLAC Task Force.

Discussion Questions:

1. What are the gaps in information on the safety, efficacy, and dosing of drugs used in pregnancy? What are the risks of not having this information? How do we determine the magnitude of benefit that this type of evidence would provide?
2. What have we learned so far from the work undertaken by PRGLAC since its inception in 2016?
3. What are the regulatory barriers to research involving pregnant people?

Session 2: Nonclinical Safety Assessment to Support Clinical Trials Enrolling Pregnant People

The results of a robust and appropriate nonclinical safety assessment are usually needed to support the inclusion of pregnant people in clinical trials. The 2018 FDA Draft Guidance on the inclusion of pregnant people in clinical trials recommends that the requirements in 45 CFR 46, subpart B are applied; ⁸ specifically, that “where scientifically appropriate, 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.”⁷ FDA's Benefit-Risk Assessment of drug or biologic applications also considers data from nonclinical studies that provide evidence of drug safety, drug exposure, and toxicities that could influence clinical trial design and conduct.¹⁵

ICH Guidance M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals outlines the types of nonclinical safety studies that are important to conduct, delineates the timing for such study conduct during drug development, and references other important nonclinical ICH guidances.¹⁶ To include pregnant people in a clinical trial, ICH M3(R2) guidance recommends that all female reproductive toxicity studies, an evaluation of safety data from previous human exposure, and a standard battery of genotoxicity tests be conducted prior to initiating the trial, in order to assess potential risk of drug exposure and to inform the trial design of such a trial regarding dosing and duration.¹⁶

In addition to describing a standard nonclinical program designed to assess the safety of a product during pregnancy, this session will address the availability of expert resources and decisional processes for study recommendations including when FDA considers it unsafe to conduct the study.

Discussion Questions:

1. If a nonclinical safety signal is observed, are clinical trials in pregnant people likely to be prohibited? What additional information could FDA rely on to inform the risk? What is needed for an optimal discussion of benefit versus risk that could lead to inclusion of pregnant people in trials when a nonclinical safety signal is observed?
2. If a nonclinical safety signal is not observed, are clinical trials in pregnant people generally considered safe to proceed? What additional information does FDA rely on to inform the potential risk?

3. It seems that a comprehensive nonclinical reproductive toxicity assessment needs to be completed and reviewed by FDA prior to conducting any clinical trial investigating therapeutics in pregnant people. This may be beyond the ability of a small research laboratory to accomplish or may delay starting early clinical trials. Are there any exceptions to this drug development pathway or is there a way to conduct nonclinical studies in parallel with clinical trials?

Session 3: Scientific and Ethical Considerations when Designing Clinical Trials that Enroll Pregnant People

Ethicists have argued that there is an obligation to conduct clinical research in pregnant people. This obligation stems from the need to provide effective medical treatment to pregnant people, to protect the fetus while administering such treatments, to prevent harms due to physician reluctance to prescribe treatments because of a dearth of information about treatment safety and efficacy, and to address concerns about fair access to research.¹ Despite the clear need for adequate evidence to support the efficacy and safety of therapeutics in pregnancy, significant challenges to conducting clinical trials in pregnant people persist.

One central challenge associated with enrolling pregnant people in clinical research is the potential of harm to the fetus.⁵ In trials of nonpregnant adults, the consideration of risks and benefits of an intervention is limited to the individual participant. In clinical trials in pregnancy, risk and benefit considerations apply both to the pregnant person and to the fetus. An intervention may offer the prospect of direct benefit to the fetus alone, the pregnant person alone, or both the pregnant person and the fetus. The same possibilities are true of drug-related risks. Often, it can be difficult to separate potential benefits and risks to the pregnant person from those to the fetus because of the interdependence of the maternal-fetal dyad. For example, if a pregnant person with a life-threatening medical condition receives an investigational drug, the fetus may experience drug-related adverse reactions but may also benefit from a potentially adequately treated maternal condition. Lastly, it is also possible that the intervention does not offer a prospect of direct benefit to either the pregnant person or the fetus. In this situation, regulations governing research supported by HHS (45 CFR part 46, subpart B) dictate that the study intervention cannot involve greater than minimal risk to the fetus, and no means other than research in pregnancy can generate the needed important biomedical knowledge.

In addition to ethics, there are a number of scientific considerations that should be examined. The physiological changes throughout pregnancy can impact a drug's pharmacokinetics resulting in clinically meaningful differences in treatment outcomes, highlighting the need for pharmacokinetic studies in pregnancy.⁵ Clinical researchers also need to consider that the potential for toxic fetal exposure to drugs can vary across the course of gestation. In the historical example of thalidomide, a dose that induced severe birth defects early in pregnancy had little to no effect on the fetus if administered later in pregnancy.¹⁷

Discussion in this session will outline factors that impact decisions to evaluate certain therapies during pregnancy, including ethical considerations, unmet need, and risk-benefit analyses. Additionally, the discussion will cover dose-finding trial designs as well as the need for long-term safety follow-up studies in children.

Discussion Questions:

1. What information regarding drug therapy is typically needed and can only be obtained in pregnant people?

2. What are the ethical considerations and scientific considerations for enrolling pregnant people in clinical trials, what are some of the major challenges?
3. How do considerations, such as the severity of the condition, unmet need, benefits, risks, and uncertainties impact the decision to enroll pregnant people in clinical trials? These considerations should include the risks of an untreated condition and the value of the information that could be obtained with research as well as the timing of enrollment and when to stop a trial in pregnancy.
4. How do we apply ethical and scientific principles to different trial designs to meet the trial's objectives?
5. What strategies could be used to advance the culture of including pregnant people in research?

Case Study: Comparing and Contrasting Clinical Trials Enrolling Pregnant People to Evaluate Treatment for a Chronic Medical Condition and Clinical Trials for a Pregnancy-Related Condition

Many people have underlying medical conditions that require treatment during pregnancy. One such example is infection with the Human Immunodeficiency Virus (HIV), which affects approximately 37.9 million people worldwide.¹⁸ According to the World Health Organization, there were approximately 1.3 million pregnant people living with HIV in 2018.¹⁹ Antiretroviral (ARV) treatment during pregnancy is important for the health of the pregnant person and for preventing perinatal transmission.¹⁹ The effects of ARVs in pregnancy have been well-studied relative to the effects of therapies for other conditions. For example, one literature review examining pharmacokinetic clinical trials noted that ARVs represented 20% of all pharmacokinetic studies in pregnancy conducted from 2008 to 2013.⁹ Even with what is known for ARVs in pregnancy, more data about the safe use of ARVs during pregnancy are needed.²⁰

Most pregnancy-related conditions are clear areas of unmet medical need. One example is fetal growth restriction, commonly defined as an estimated fetal weight less than the 10th percentile for gestational age. Fetal growth restriction results from suboptimal uterine-placental perfusion and fetal nutrition. There are many potential etiologies for the condition, including maternal medical conditions, multiple gestation, infectious diseases, and placental disorders.²¹ There are no approved drug therapies for the prevention or treatment for intrauterine growth restriction, although aspirin or various dietary and nutritional supplements have been studied.

This session will be divided into two case studies. The first will explore ethical and trial design considerations for a hypothetical study of an HIV therapy in pregnant people. The second case study will explore a hypothetical clinical trial to determine the safety and efficacy of a drug for the treatment of fetal growth restriction.

During the discussion, panelists will use these case studies to illustrate the ways in which disease severity, unmet medical need, and data needed to support the conduct of clinical trials in pregnant people may address scientific, ethical, and regulatory considerations during drug development.

Discussion Questions:

1. How do the clinical context and study objectives impact the design of a trial (for example, how do clinical investigators consider the clinical context and study objectives when choosing whether to implement a single arm or placebo controlled study)?
2. What effects do the physiologic changes throughout pregnancy have on drug metabolism and how does that affect the study design? How do considerations related to the duration of treatment and trimester of pregnancy (e.g. vulnerability of the fetus) affect the study design?

3. How does the condition influence potential endpoints/outcomes we consider for the pregnant person, neonate, and older infant?

Session 4: Challenges and Next Steps

This final session will cover key takeaways from the workshop. Discussion will also highlight the outstanding challenges associated with conducting clinical trials in pregnant people, including funding, scientific, and regulatory barriers, and challenges associated with the existing clinical trial infrastructure and medicolegal risks, with the goal of identifying feasible and actionable next steps to promote and facilitate the enrollment of pregnant people in clinical research.

Discussion Questions:

1. What current resources exist to assist clinical investigators in obtaining feedback on the robustness of their nonclinical and clinical data prior to proceeding with IND submissions for clinical trials enrolling pregnant people?
2. What are the priority conditions impacting pregnant people that should be addressed first? What are the short term and long term goals of clinical trial conduct and therapeutic development in these areas?
3. How can industry, academia, regulatory stakeholders and, NIH best collaborate to make progress in therapeutic development for conditions impacting pregnant people? What are the opportunities for public-private partnership to drive this work forward?
4. What are the greatest challenges and what are potential solutions to the conduct of clinical trials during pregnancy?
5. How do we foster education and awareness about available resources, requirements, and options for participating in clinical research [for researchers, healthcare providers and pregnant people]?

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