Duke | MARGOLIS CENTER for Health Policy

Advancing Drug Development for the Prevention of Spontaneous Preterm Birth

Virtual Public Workshop
January 23-24, 2024 | 1:00 – 4:30 pm EST

Discussion Guide

Introduction

Each year, 1 in every 10 babies is born preterm in the U.S., and complications from preterm birth (PTB) are the leading cause of infant mortality globally.[1] Preterm babies who survive may often face short- and long-term medical complications. Infants born premature have four times the average first-year medical costs compared to those delivered full-term, and PTB exacts an economic cost of $25.2 billion in the US each year.[2] Despite the significant impacts and burden, there is a lack of therapy for preventing PTB.

Most preterm births that occur are spontaneous, and the causes are not well understood. This has made it difficult for researchers to identify effective tools and therapies to prevent spontaneous preterm birth (sPTB). Furthermore, conducting studies on preterm birth prevention is wrought with challenges, including inadequate understanding of etiologies of PTB, lack of standardized guidelines for the clinical management of PTB, ethical concerns, insufficient understanding of regulatory standards and requirements, and limited use of real-world data.

Because these challenges hinder research and drug development for PTB prevention, there is a significant unmet need for therapies to prevent sPTB. In 2011, the US Food and Drug Administration (FDA) approved the first therapy for the prevention of recurrent preterm birth under an accelerated approval pathway. However, in 2023 after thoughtful consider by FDA, the decision was made to remove this drug from the market after a post market confirmatory study failed to verify clinical benefit.[3] This has left clinicians without an FDA-approved therapy to prevent sPTB. Despite the absence of treatments, the pipeline for new products to prevent sPTB remains stagnated and pharmaceutical interest continues to lag due to the regulatory, ethical, and legal risks to conducting trials on sPTB and a lack of incentives.[4]

The Duke-Margolis Center for Health Policy, under a cooperative agreement with the FDA, is convening this public workshop to promote discussion and collaboration between researchers, clinicians, industry, parents, and regulators on considerations for advancing drug development for the prevention of sPTB. The workshop aims to bring a multidisciplinary group of experts and individuals with lived experience together to generate ideas and discussion. The topics covered in this two-day virtual meeting include:

- the current landscape and understanding of PTB,
- the ethical and regulatory considerations in the clinical development of products,
- the impact preterm birth has on families,
- evaluating efficacy and safety in clinical programs, and
- considerations for dose-finding and designing clinical trials.

Session 1: Current Understanding of Preterm Birth

Preterm birth is defined as delivery before 37 completed weeks of gestation.[1] Gestational age is a key defining factor for preterm delivery and also for subcategorizing preterm births (i.e., extremely preterm, very preterm, moderate to late preterm).[5] It is therefore important to have accurate tools for measurement. There are a few methods for determining gestational age, but most rely on the date of last menstrual period, prenatal ultrasounds and observation of fetal growth and development.[6] Such measures are important for understanding the etiology, mechanism, and causes of PTB, which may also support identification of potential therapies for prevention.

PTB is most often the result of spontaneous preterm labor, although babies may also be born preterm because there is a medical indication to induce labor or have an early caesarean birth. Given different etiologies and lack of standardized management, it is also difficult to identify those who are at risk of sPTB. Several demographic risk factors have been identified such as maternal age, birth spacing, smoking, obesity, health insurance coverage, and socioeconomic status.[2] In the US, there are also disparities in preterm birth rates among different ethnic and racial groups, with the highest rates in Black infants (14.4%).[2]

Preterm birth not only affects the mother and infant, but also has a significant societal impact. Medical care expenses for preterm infants were the biggest contributor to the cost ($17.1 billion) from hospitalization and specialized care, and over 90% of the expenses incurring during the infant's early years.[7] Beyond medical care, educational and early intervention services for preterm infants accounted for approximately $1.3 billion in expenses.[7]

In this session, speakers will give presentations on the epidemiology and social impacts of spontaneous preterm birth and provide an overview of the current understanding of the etiologies and pathophysiology of preterm birth, and current tools and methods used to predict spontaneous preterm birth.

Session 2: Ethical and Regulatory Considerations for Clinical Development Programs for Products Intended to Prevent Preterm Birth

Studying treatments in pregnant women has long posed a number of ethical concerns and challenges for researchers – not only do they have to consider the safety and efficacy of the drug in the mother, but also its impact on the fetus. This has often led to pregnant women being excluded from clinical trials. However, this poses a significant, global issue for conditions related to pregnancy, such as sPTB, and has resulted in a high unmet need for therapies for such conditions.

Despite willingness from women to participate in trials, regulatory requirements can present hurdles as well.[8] In 2018, the FDA issued draft guidance entitled *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* which is intended to facilitate discussion across stakeholder groups to promote maternal and fetal health and to inform prescribing decisions during pregnancy. FDA acknowledges the challenges of including pregnant women in drug development research, outlines the interdependencies of maternal and fetal well-being, and provides recommendations for inclusion of pregnant populations based on ethical principles and clinical need.[9]

In this session, experts will provide a series of presentations on regulatory considerations including the process of evaluating efficacy and safety of investigational products, the ethical considerations for clinical trials in pregnant persons, and the unique challenges to developing therapies for preterm birth prevention.

Session 3: Impact of Preterm Birth on Families and Society

Preterm birth has both immediate and lasting impacts on the infant, family, and society as a whole. In the immediate period, preterm infants face a host of health complications, including respiratory distress syndrome, infections, and feeding difficulties. These challenges can require extended hospital stays and specialized care, placing significant emotional and financial stress on their families. Even after discharge, infants face considerable risk of neurodevelopmental issues, learning disabilities, and chronic health conditions that can persist long into their lives.

The impact of preterm birth goes beyond just the infant's life, as the family and caretakers are significantly affected. Parents often experience considerable emotional distress and anxiety due to their child's health struggles, coupled with the financial strain of medical expenses and potential loss of income from taking time off of work to care for their preterm infant.[10] Navigating the complex medical and developmental needs of their child – from coordinating medical appointments, therapies, and daily care – places an immense pressure on parents and caregivers.

This session will feature the experiences and perspectives from parents of preterm infants and professionals who work with parents and families affected by preterm birth. The panelists will highlight the short- and long-term challenges and impacts of caring for children born preterm.

Discussion Questions:

- What are the primary challenges that most impact the baby, mother, and family while in the neonatal intensive care unit (NICU)? What are the key challenges for baby and family after discharge?
- What are the greater impacts to the family and community when a baby is born preterm?
- What resources are needed and available to a parent and family?
- What long-term challenges can arise from giving birth preterm and from being born preterm (e.g., physical, developmental, social)?
- What health outcomes for both the mother and baby would you consider most important following a preterm birth, both in the short-term and long-term?
- What recommendations from a patient/family-centered perspective would you give researchers developing therapies for the prevention of preterm birth? What types of outcomes are considered meaningful to parents and families (e.g., changing gestational age/low birth weight [GA/LBW] categories, reduced NICU morbidities, impact on long-term outcomes)?

Session 4: Assessing Efficacy and Safety in Clinical Programs for Therapeutics for Preterm Birth Prevention

For a new therapeutic to gain FDA approval, studies must demonstrate that the drug's benefits outweigh any associated risks. When considering drugs for maternal conditions, such as prevention of preterm birth, researchers have the added challenge of demonstrating efficacy and safety for both the mother and the neonate. This means the drug must be proven safe for both the mother and fetus, while also

demonstrating efficacy in preventing preterm birth. Selecting appropriate outcome measures is therefore paramount to conducting studies for PTB prevention.

Gestational age at birth is a commonly used outcome because it significantly affects neonatal survival and morbidity. However, other neonatal and maternal outcomes may also be essential to consider. Examples of maternal outcomes include maternal morbidity and maternal infection, and examples of neonatal outcomes include mortality, birth weight, respiratory morbidity, and neurodevelopmental morbidity.[11] Some researchers have taken steps to address the challenge of selecting outcome measures by developing a core outcome set (COS) for evaluation of interventions to prevent preterm birth.[11] Tools like a COS can support consistency and comparability across trials. However, implementation of these outcome measures can pose a number of challenges to researchers.

The panelists in this session will discuss efficacy and safety assessments used in clinical programs as well as opportunities to improve and address the challenges within these programs. The discussion will also consider how researchers can identify clinically relevant neonatal outcomes.

Discussion questions:

- Are the current approaches to measuring efficacy sufficient and are the endpoints meaningful?
- Why is gestational age alone not a sufficient outcome measure for demonstrating efficacy of a product intended to prevent preterm birth?
- What neonatal outcomes would you recommend assessing for clinical trials on prevention of preterm birth?
- What are important factors to consider when evaluating a product's safety?
- How do different underlying causes and mechanisms of preterm birth impact interventions?
- How is the optimal time to start and stop the intervention determined?

Session 5: Dose-Finding and Clinical Trial Design Considerations

Despite the large impact of preterm birth, there is a dearth of research and funding dedicated towards identifying new therapeutic options and conducting clinical trials for the prevention of preterm births.[12] The lack of consensus in clinical priorities of new products has also contributed to stalled product development. Surveys on target product profiles for therapy to prevent PTB have noted several key considerations including, but not limited to, the appropriate gestational age, maternal risk for PTB, etiology of PTB, clinical efficacy (perinatal and neonatal), and level of treatment adherence.[13] Studies must take these considerations into account while collecting the necessary data on safety and efficacy, as discussed in the prior session.

Researchers designing trials for PTB prevention therapies also face challenges with identifying the appropriate study populations and recruiting patients for the trials. The multifaceted risk factors and unknown causes of spontaneous preterm birth can make it difficult to know which pregnant persons are at risk. As a result, studies will often focus on those who have a prior history of PTB, but this leaves out women with other associated risk factors.

In this session, experts from the FDA will have the opportunity to share their perspective on the importance of identifying the appropriate dose of a drug for development and the data needed to support clinical trials for both novel and approved products, emphasizing consideration of different study populations and control groups in clinical trials. Experts with experience conducting clinical trials will

have the opportunity to discuss these important themes with the other FDA speakers. They will also discuss dose finding while considering physiologic changes in pregnancy and drug metabolism.

Discussion questions:

- What kinds of nonclinical data are needed to support clinical trials for novel products versus repurposed products (i.e., products already FDA-approved for other indications)?
- How can using different study populations create better clinical trials?
- What constitutes an appropriate control group for these trials?
- How do physiological changes in pregnancy and drug metabolism affect dose finding for preterm birth prevention therapies? How could we address the lack of standardization for disease risk, severity, and progression for common diagnoses?
- How can we manage the heightened concern when dealing with any drug that has a potential effect on the fetus and on the mother?
- What are special considerations in recruitment of high-risk individuals for sPTB?
- Are there any special considerations for obtaining informed consent for research involving the evaluation of investigational products for the prevention of pre-term birth?

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[1] WHO | Fact Sheets| Preterm birth
[2] March of Dimes | Prematurity Profile
[3] FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena
[4] Addressing a broken drug pipeline for preterm birth: why early preterm birth is an orphan disease | American Journal of Obstetrics and Gynecology
[5] Preterm Birth | Maternal and Infant Health | Reproductive Health | CDC
[6] Landscape of Preterm Birth Therapeutics and a Path Forward - PMC (nih.gov)
[7] Preterm birth lifetime costs in the United States in 2016: An update - PMC (nih.gov)
[8] Scientific, ethical, and legal considerations for the inclusion of pregnant people in clinical trials | American Journal of Obstetrics and Gynecology
[9] FDA | Draft Guidance | Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
[10] The impact of preterm birth <37 weeks on parents and families: a cross-sectional study in the 2 years after discharge from the neonatal intensive care unit | Health Qual Life Outcomes
[11] A Core Outcome Set for Evaluation of Interventions to Prevent Preterm Birth - PMC (nih.gov)
[12] New medicines for spontaneous preterm birth prevention and preterm labour management: landscape analysis of the medicine development pipeline - PMC (nih.gov)
[13] Expert consensus on novel medicines to prevent preterm birth and manage preterm labour: Target product profiles - PubMed (nih.gov)