FDA Perspectives on Trials in Pregnant and Lactating Women

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The speaker has nothing to disclose.

Overview

- Introduction
- Clinical Trials in Pregnant Women
- Clinical Trials in Lactating Women
- Key Messages

Introduction

- FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation
- FDA's Role in Public Health of Pregnant and Lactating Women
  - Seeks to obtain appropriate dosing and safety information on the drug from all sources
  - Seeks safe and effective drugs for pregnant and lactating women
  - Supports the conduct of research as long as clinical trials are appropriately designed and mother and fetus/infant are protected
  - Plans to harmonize with the revised Common Rule to the extent possible

Clinical Trials in Pregnant Women

Ethical Considerations

- Development of accessible treatment options for the pregnant population is a significant public health issue
- Trials designed to minimize risk as much as possible while preserving the ability to achieve research objectives
- Drug sponsors should consider an ethicist in the planning of these trials

Ethically Justifiable to Include Pregnant Women

- 45 CFR Subpart B: Ten conditions need to be met, including:
  - Nonclinical studies (including pregnant animals) have been completed
  - Clinical studies, including studies in nonpregnant women, have been conducted
  - Trial holds out the prospect of direct benefit to the pregnant woman or the fetus
  - If there is no prospect of benefit, the risk to the fetus is not greater than minimal

Pharmacokinetic (PK) Trials

- Enroll pregnant women for whom the drug is prescribed for a medical condition in the clinical setting, or those (woman and/or her fetus) who may potentially derive direct benefit from the research-related intervention.
- Consider PK trials when …
  - The drug is known to be prescribed in or used by pregnant women, especially in the second and third trimesters.
  - For a new drug or indication, if there is anticipated use of the drug in pregnancy.
  - Use in pregnancy is expected to be rare, but the consequences of uninformed dosages are great (e.g., narrow therapeutic range drugs, cancer chemotherapy).
  - Pregnancy is likely to alter significantly the PK of a drug (e.g., renally excreted drug) and any of the above apply.

Women Who Become Pregnant While Enrolled in a Trial

- Unblinding that pregnant patient -- to allow for counseling regardless of exposure to study drug or control
  - Risk of ongoing drug exposure
  - Risk of untreated maternal disease
- If a women decides to continue in trial, a second informed consent is recommended
- Follow up to obtain the pregnancy outcome

Useful FDA guidance on unblinding:

- Guidance to Industry "E9 Statistical Principles for Clinical Trials"
- Guidance to Industry "E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting"

Clinical Trials in Lactating Women

Ethical Considerations

- Consider only those risks and benefits to the lactating woman and her breastfeeding infant that may result from research participation (21 CFR 56.111(a)(2))
- When you consider exposure to the breastfed infant a risk, research must not involve "greater than minimal risk" (21 CFR 50.51), unless the research would provide generalizable knowledge about the child's disorder or condition (21 CFR 50.53)
  - When the drug is medically necessary for the lactating woman, may be important for understanding effects of drug exposure on the breastfed infant because infant has a condition of ongoing drug exposure through continued breastfeeding with its associated risks.

Three Populations of Women to Consider for Participation

1. *Clinical Setting:* Lactating women who are prescribed a drug for a medical condition in the course of routine clinical practice
   - Decision to use drug clearly separate from enrollment in lactation study
   - Drug exposure to infant is “clinical risk”
   - Woman decides if breastfeeding continues

Three Populations of Women to Consider for Participation

2. *Research Setting, Subjects with Medical Condition:* Lactating women who are prescribed an investigational drug for a medical condition in the research setting
   - Potential infant exposure is "research risk", offers no clinical benefit to infant
   - Infant must not be exposed to breast milk with investigational drug
   - Breast milk samples could be provided for PK analysis
3. *Research Setting, Healthy Volunteers:* Lactating women who are healthy volunteers and are prescribed investigational drug solely for research purposes
   - Infant must not be exposed to breast milk with investigational drug
   - Breastfeeding could be resumed after the study

All Clinical Lactation Studies should. . .

- Separate the maternal decision to use a medically necessary drug from the decision to participate in a clinical lactation study
- Define the risks to the breastfed infant that occur only as a result of the research
- Obtain informed consent from the lactating woman

Key Messages

Key Messages

FDA supports conduct of clinical trials

- when appropriately designed and mother and fetus/infant are protected
- If no prospect of direct benefit:
  - Risk to the fetus/infant is not greater than minimal risk
  - Opportunity for trials in the clinical setting, where women are using the drug therapeutically

FDA utilizes safety data from across the research continuum to improve health outcomes for pregnant and lactating women, and their fetuses/infants

- PLLR (Pregnancy and Lactation Labeling Rule) format includes update of safety information
- Need data to better inform drug dosing and safety information

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