CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

# Recommendations for Pregnancy Testing in Clinical Trials

**July 2017**

**CTTI MISSION:** To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

Clinical Trials Transformation Initiative. Recommendations for pregnancy testing in clinical trials. Published August 2017. https://ctti-clinicaltrials.org/our-work/quality/pregnancy-testing/

## INTRODUCTION

Many clinical trials include a plan for testing women for pregnancy because of the possibility that a developing embryo/fetus could be harmed by the study intervention. Detecting a pregnancy as early as possible, ideally before study enrollment or very early in the pregnancy, prevents or limits embryo/fetal exposure to potentially harmful study interventions. However, there are no specific guidelines about how to test for pregnancy in clinical trials. Wide variation in pregnancy testing plans leads to: 1) potential for inadequate protection against embryo/fetal exposure and/or unnecessary burdens on study participants and 2) inefficiencies caused by disagreements between sponsors, investigators, and regulators.

The project team conducted a stakeholder survey, created a computer simulation model, and held an expert meeting. The purpose was to better understand current risk assessment, suggest a method to estimate the outcomes of different pregnancy testing plans, and then develop guidelines for pregnancy testing in clinical research.

The team found that current practice varies greatly, with a general lack of formal consideration of the potential embryo/fetal risks of specific study interventions and the likely outcomes of the chosen pregnancy testing plans in specific patient populations.

The following recommendations apply to clinical trials where pregnancy testing is considered necessary because there is a possibility of pregnancy in the study population and embryo/fetal exposure to the study treatment (intervention or control) poses a known or unknown risk:

## CTTI RECOMMENDATIONS

## 1. Recommendations for investigators and sponsors in developing a clinical trial protocol:

### a. The protocol should clearly state the specific purposes of pregnancy testing in the research study.

- Prevent or minimize embryo/fetal exposures to study drug/intervention by
  - Confirming non-pregnant state at time of enrollment and, when applicable, prior to any subsequent exposures
  - Detecting early pregnancies to determine whether to continue participation in the study

### b. The protocol should describe the procedure for handling positive or indeterminate pregnancy tests.

- Define a positive test as it relates to the specific pregnancy testing plan (actual measured level of hCG that is considered positive)
- Define an indeterminate test (level of hCG, which will vary by study population age and underlying medical condition, and type of pregnancy test used)
- Define:
  - Procedures for follow-up testing and evaluation of both positive and indeterminate tests
  - Procedures for continuing, holding, or stopping study interventions and appropriate medical follow-up in the event of positive or indeterminate test results (based on the potential embryo/fetal risks of exposure to study interventions and the potential benefit to the participant from continued study participation)

## 2. Recommendations for investigators when developing a pregnancy testing plan:

**a. Assess the balance of pregnancy testing plan advantages (reduced risk of embryo/fetal exposure) versus burdens (participant burden, study team workload, costs). This can be done using:**

- Formal quantitative methods incorporating parameters including age of study population, type of contraceptive methods used by the study population, type of pregnancy test used and its detectable threshold of hCG, and the proposed timing of testing during the menstrual cycle to estimate
  - The negative and positive predictive values of a proposed testing strategy
  - The absolute differences in exposures prevented based on variable testing options
- Alternatively, a semi-quantitative or qualitative assessment of risks and burdens considering the same factors

**b. Assess participant burdens regarding the likelihood of false negative results and unintentional embryo/fetal exposure, and likelihood of false positive results.**

- Invasiveness of testing (serum versus urine tests)
- Timing of testing (random versus timed to the menstrual cycle) and study interventions
- Implications of false positives (repeat testing, delay in receipt of study interventions, study withdrawal, anxiety/worry) for the patient

**c. Avoid participant-administered home pregnancy tests in clinical trials.**

- Although patient-administered tests offer convenience to both participants and study staff, disadvantages include:
  - Consistent evidence of observer variability in interpretation of consumer pregnancy test results
  - Potential for emotional distress in event of participant-read false negative result and subsequent embryo/fetal exposure
  - Potential for desire to continue in study affecting interpretation of ambiguous test results

## 3. Recommendations for the informed consent process*

**a. Clearly articulate the extent of knowledge about potential embryonic or fetal risks from exposure to study intervention.**

- Acknowledge that:
  - Pre-clinical testing in animals may not fully inform assessment of risk in humans
  - Even when clinical trial and/or post-market data are available, overall knowledge about potential embryo/fetal risks may be minimal

**b. Clearly explain the limitations and consequences of pregnancy testing to participants. Include the following:**

- Potential for false negatives
  - No available test will detect 100% of pregnancies
- Potential for false positives (including "indeterminate" results)
  - False positive tests are possible in non-pregnant patients
  - The likelihood of a positive or indeterminate test varies based on patient age, other conditions, and type of test
- The implications of a positive or indeterminate test for study participation
  - What additional tests/procedures will be performed to confirm a pregnancy?
  - Who decides on whether to continue or terminate study participation?
  - What criteria will be used to make that decision?
  - How will pregnancy outcomes be followed?
  - Who is responsible for ensuring patients will have appropriate follow up?

* Acknowledging efforts to simplify the informed consent form, these recommendations apply to the consent process. For example, a separate concise information sheet could be created for females of reproductive potential or if desired included in the consent form as a separate page for females of reproductive potential only.

## ABOUT THE RECOMMENDATIONS

- These recommendations are based on results from CTTI's Pregnancy Testing Project.
- CTTI's Executive Committee approved on July 24, 2017.
- Funding for this work was made possible, in part, by the Food and Drug Administration through grant R18FD005292 and cooperative agreement U19FD003800. Views expressed in written materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. Partial funding was also provided by pooled membership fees from CTTI's member organizations.
- All of CTTI's official recommendations are publicly available. Use of the recommendations is encouraged with appropriate citation.

## ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI)—co-founded by Duke University and FDA—is a public-private partnership whose mission is to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based therapeutic prevention and treatment options.