



## Pregnancy Testing in Clinical Trials

Summary of an Expert Meeting held July 15 & 16, 2013

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***Clinical Trials Transformation Initiative (CTTI)***  
***July 15 & 16, 2013***

**Meeting Objectives**

On July 15-16 2013, the Clinical Trials Transformation Initiative (CTTI) invited representatives from a broad cross-section of the clinical trial enterprise, including regulators, government and industry sponsors of clinical research, academic and non-academic research institutions, patient advocates, and other interested parties to an expert meeting held in Bethesda, MD. The key objectives of this meeting were to:

- Present survey findings and computer simulation model results from the CTTI project entitled, *Developing Rational Guidance for Pregnancy Testing in Clinical Trials*
- Discuss practices and challenges in assessing the acceptable risk of pregnancy and implementing a pregnancy testing protocol for a clinical trial
- Solicit additional feedback and develop consensus on factors to consider when assessing acceptable risk of pregnancy in clinical trials

**Overview of the *Developing Rational Guidance for Pregnancy Testing in Clinical Trials* Project**

Pregnant women are excluded from many, if not most, clinical trials. Although there are several potential scientific justifications for this exclusion (such as the often unknown effects of the normal physiological changes of pregnancy on drug metabolism), the primary rationale is to minimize the risk of adverse fetal effects from exposure to study-related interventions. Little formal guidance is available from regulators on how to develop pregnancy testing protocols for clinical trials. Designing such a protocol requires balancing the performance characteristics of a given test, the baseline risk of pregnancy in a given subject population, the potential risks to the fetus from study interventions, and the effect of the testing protocol on overall study implementation in terms of burden to subjects, burden on staff, and direct costs. There are no published data on the consistency of sponsors, investigators, or institutional review boards (IRBs) in applying these criteria to designing and evaluating pregnancy testing protocols. However, anecdotal reports indicate that there is widespread variability. Development of evidence-based guidance that explicitly considers the level of acceptable risk to suggest appropriate pregnancy testing protocols will ultimately improve protection of research subjects, reduce the risk of unintended fetal exposure, and reduce the workload of sponsors, investigators, IRBs, and other stakeholders in the clinical trial enterprise.

In an effort to address these issues, the CTTI has been working on the project *Developing Rational Guidance for Pregnancy Testing in Clinical Trials*. The goals of the project are to obtain an understanding of stakeholders' current practices a targeted survey; to summarize these practices as well as other salient issues; and to integrate this information into the development of recommendations and tools for creating rational pregnancy testing protocols.

## Expert Meeting

At this Expert Meeting, we reviewed the basics of embryology and teratogenic risk, highlighting the baseline risk of anomalies, frequency of early pregnancy loss, and the preponderance of woman of reproductive age in clinical trials, often with drugs or devices of unknown risk. Given this background, our discussions throughout the day centered around the two main goals of pregnancy testing in clinical trials – to prevent exposure during pregnancy and to minimize exposure. Although contraception was noted as an essential part of the prevention process, that was not the focus of our efforts. We also reviewed the poorly understood topic of pregnancy testing, focusing on the multiple variants of hCG and how this influences sensitivity and specificity of testing and results in a lack of standardization between assays, be they lab-based or point-of-care tests. Specific situations with misleading test results (the “variant hook” effect in late pregnancy, elevated levels during peri-menopause) were also reviewed, with special attention paid to early testing, prior to the ability to detect a pregnancy. The regulatory process for evaluating pregnancy tests was detailed. Pregnancy tests are class II (moderate risk) devices that undergo 510(k) regulatory clearance and must show substantial equivalence to predicate device. The FDA-approved sensitivity threshold (lower limit of assay) represents the hCG level where the proportion of approximately 100 tests yield a positive result 50% of the time and a negative result 50% of the time. Post-market surveillance indicates pregnancy test devices are accurate, with few false positive and/or false negative results generally reported. With this background in mind, one pharmaceutical industry perspective was presented, highlighting the lack of guidance around these issues, despite the complex patient safety and operational issues at stake.

Evan Myers, the academic team lead for the project, then presented findings from the stakeholder survey, the project’s effort to understand generally accepted levels of risk, as well as current practices. The web-based survey was sent to 58 individuals, with a response rate of 60%. The most notable findings discussed were that 50% of respondents reported the maximum acceptable risk of pregnancy as <less than 1/10,000, but chose testing options that were inconsistent with that standard. Testing characteristics deemed to be most important were negative predictive value and patient burden. These findings were used as a discussion point for recognizing our desire for an unachievably low level or risk, as well as our discrepant beliefs in acceptable risk and testing practices.

After describing survey findings, a model was presented as a possible tool to help select pregnancy testing protocols within a particular study. The model serves as an interactive method to synthesize vast amounts of information and estimate likely outcomes of different decisions (when to test, type of test, etc.). Using numerous micro-simulations, the model factors in population specific factors – age distribution, contraceptive use, history of hysterectomy, day of last menses, per-cycle fertility rates – to calculate a risk of pregnancy and the likelihood of detecting a pregnancy. Population parameters as well as testing strategies (sensitivity of test, day of testing, frequency of testing) can be altered to fit protocol specifics. As anticipated, the model predicts fewer pregnancies with increasing age and decreasing pregnancy detection when testing is not timed to menses. Of particular interest was the finding that absolute differences in pregnancy detection rates were relatively small when comparing between highly sensitive (serum) and less sensitive (urine) pregnancy tests. Discussion focused around possible

changes to the model to address additional concerns such as disease-specific fertility changes and cost. The model can estimate the negative predictive value (NPV) for a given trial population

and testing protocol, but whether it is acceptable depends on the degree of risk of exposure. One of the major problems is that it's very difficult to estimate the risk except for a few classes. The recommendation was that the model be seen as an evidence-based tool to help calculate risk, but that the judgment about acceptable level of risk would still need to be determined by the model user.

With the goal of summarizing the meeting's discussions and producing user-friendly tools for developing rational testing protocols in pregnancy, the following documents are anticipated:

- General guidelines around pregnancy testing in clinical trials incorporating basic reproductive biology and testing performance to allow the standardized application of consistent and evidence-based principles to specific trials
- Project summary and peer-reviewed publication describing guidelines and modeling process