CTTI_Pregnancy_Testing_Project_Protocol

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ABSTRACT

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 on how to develop pregnancy testing plans for clinical trials. To address this issue, the Clinical Trials Transformation Initiative (CTTI) conducted a project - which included an online survey, a quantitative model, and a meeting of content experts and stakeholders - to develop recommendations for pregnancy testing in clinical research based on currently available evidence. This protocol describes the project methods.

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Document body

Project Summary

Pregnancy Testing in Clinical Trials

1. **Background, Objectives, and Study Procedures**

Background:

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 guidelines for clinical trials.

A pregnancy testing protocol is defined by

- Type (or types) of pregnancy test—serum, urine performed by lab, point-of-care testing performed by medical personnel, point-of-care home testing performed by subjects
- Frequency of testing: prior to study intervention only, prior to study and at regular intervals throughout study, prior to, during, and post study intervention
- Timing of testing relative to potential conception (practically, relative to expected menses): Random, specified within a variable time period

The negative predictive value (NPV) — the reassurance that a subject is not pregnant—of any pregnancy testing protocol is a function of (1) the likelihood that the subject is actually pregnant, and (2) the likelihood that a given test will detect hCG in a pregnant subject. However, these principles are not addressed in guidance documents. This leads to variable protection for subjects, decreased efficiency for sponsors, investigators, and IRBs.

Objectives:

- To obtain a deeper understanding of current practices:
- for defining the acceptable risk of pregnancy in a clinical trial population
- for determining which factors, in addition to fetal risk, are considered when choosing a pregnancy testing protocol

- To facilitate an informed discussion of practices and challenges in assessing the acceptable risk of pregnancy and implementing a pregnancy testing protocol
- To issue recommendations for future approaches based on consensus on acceptable risk of pregnancy:
- Under different scenarios (e.g., category C versus category X study drug) and desired negative predictive value of testing protocol
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- Estimate NPV of different combinations of classes of pregnancy tests, timing and frequency of testing
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- Pregnancy testing protocols to achieve stated levels of acceptable risk
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Conduct of Study (Study Procedures):
The first objective is to gain a deeper understanding of current practices for defining the acceptable risk of pregnancy in a clinical trial population and for determining which factors, in addition to fetal risk, are considered when choosing a pregnancy testing protocol.

Methods:
1. The CTTI Pregnancy Testing in Clinical Trials Working Group is composed of stakeholders from academia, the pharmaceutical industry, the Food and Drug Administration, and patient advocates.
2. The principal investigator in collaboration with the working group will develop a survey (attached as Appendix A) to assess factors that are currently used in designing pregnancy testing protocols. The survey consists of different clinical trial scenarios and asks the respondents to provide an estimate of the acceptable risk of unintended fetal exposure over the course of the study (e.g., 1 in 100, 1 in 1000, 1 in 10,000); to rank the relative importance of negative predictive value, subject burden, study team burden, and testing cost; and to describe the basic type of testing protocol (in terms of type of test, timing of test, and frequency of testing) recommended for that scenario.
3. The survey content will be used to create an online survey using Qualtrics Survey Software (duke.qualtics.com).
4. Central CTTI staff will work closely with the working group to identify survey audience from CTTI membership organizations and referrals from CTTI members to other clinical trials professionals
5. The online survey will be emailed to the survey audience.
6. The principal investigator and CTTI staff will compile and analyze anonymous survey responses and share summary with the working group.
7. In parallel with conducting the survey, the principal investigator will generate a model to estimate expected rates of false negative and false positive pregnancy tests during clinical trials as a function of age and contraceptive usage by subjects, type of pregnancy test, frequency of testing, and timing of testing relative to conception. The model will be created using data in the published literature, regulatory filings, and package inserts.

The second objective is to facilitate an informed discussion of practices and challenges in assessing the acceptable risk of pregnancy and implementing a pregnancy testing protocol.

Methods:
1. Conduct an expert meeting, including partners engaged in projects related to pregnancy testing in clinical trials, key stakeholders, and CTTI members. Findings from the survey and model will be presented and issues in assessing the acceptable risk of pregnancy and implementing a pregnancy testing protocol will be discussed.
2. Develop consensus on factors to consider when assessing acceptable risk of pregnancy in clinical trials.

The third objective is to issue recommendations for future approaches based on consensus on acceptable risk of pregnancy.

Methods:
1. Synthesize results of expert meeting and develop recommendations.
2. Develop tables and/or tool to compare NPV under different scenarios of subject risk, choice of hCG test class, testing timing and frequency

1. **Subject Population:** Approximately 100research professionals who design or provide regulatory oversight for protocols which include females of reproductive potential and exclude women who are pregnant. Email addresses of research and regulatory professionals will be identified by contacting the Steering Committee representatives (https://www.ctti-clinicaltrials.org/about-us_main/organization/steering-committee) from relevant CTTI member organizations. In addition, CTTI representatives or project working group members may refer non-CTTI members to participate in survey. We will send an email to potential survey respondents describing the purpose of our study and inviting them to participate (email attached as Appendix A).

1. **Risks and Benefits** There are no physical risks involved in this study. The primary risk to participants in any phase of this study is to the confidentiality of the information shared about the survey results. This risk will be minimized using the procedures described in Section 4. Given the nature of the research questions, even in the unlikely event of participants' responses being disclosed in identifiable form outside the research, subjects would not be at risk of criminal or civil liability nor of damage to their

financial standing, employability, or reputation. There are no direct benefits to participants for participating in this study; however, we expect that the successful completion of our study will provide important data that will assist in developing evidence-based recommendations for pregnancy testing protocols in clinical trials. These guidelines will lead to increased protection for subjects, and increased efficiency for sponsors, investigators, and IRBs.

1. **Data Collection and Confidentiality:** The invited survey respondents names and email addresses will be loaded into the Qualtrics Survey Software by CTTI Core staff. Survey responses will be anonymous with no link to names or email addresses of respondents. The duke.qualtrics.com website is only accessible with a valid Duke University Net ID. The invitee list will be kept on password secure computers at the Duke Clinical Research Institute (DCRI). The following describes DCRI data storage and security procedures, which are designed to maintain the confidentiality of research data:

By restricting access to confidential data, the DCRI Network Infrastructure serves as the principal means of safeguarding information from improper use or disclosure. Remote Access at the DCRI is granted by one of two methods. The first method is a VPN (Virtual Private Network) connection. A VPN allows users to form an encrypted network connection via the Internet backbone. This is an extremely secure connection because it utilizes several cryptography algorithms. The second method is Citrix access. Citrix clients use an ICA (Independent computing architecture) client. Once again, all connections are encrypted. Client and server data is secure while the connection is maintained. These technologies are in place at DCRI and are fully functional.
Points of internal access to DCRI databases are monitored and maintained by a firewall and router. At point of entry at the firewall we have a policy which denies or accepts certain types of Internet traffic from specific sponsors or sources. Connections to certain sites are also restricted. The router has access lists and commands to deny or permit traffic. All users are authenticated, authorized, and accounted for on the DCRI domain. The domain is password protected. All passwords change every 90 days, these passwords are a minimum of 6 characters and passwords cannot previously used (4 old passwords are cached). All file and directory access is controlled by groups and users rights. Users must have the proper access rights to read, create, and modify files. In addition, only key-card access is permitted within the DCRI. Secured waste receptacles are available on each floor for expired confidential printouts; this waste is shredded weekly.
Participants' names and email addresses will not be linked to their survey responses (responses will be anonymous). The email invitation will request that respondents do not identify themselves in any of the free text responses provided in the survey. The online survey software will allow for anonymous results while still allowing for targeted follow-up of non-respondents by automatically emailing only those invitees who have not responded after specified time periods.

1. **Consent Process:** We believe this research may be eligible for exemption, in which case informed consent would not be required.