Pregnancy During Participation in Research

Spectrum Health IRB Guidance Document

Purpose

In accordance with the principle of *justice* outlined in the Belmont Report, a person of childbearing potential (POCBP) and pregnant persons must not be excluded from research without appropriate medical or scientific justification.

The purpose of this document is to provide guidance to investigators, study teams, and IRB staff/members on several scenarios in which pregnant persons, pregnant minors, and POCBP may be included in research, either coincidentally or as a targeted study population, when investigational treatment is included. Federal regulations do not distinguish between research in which POCBP are a targeted population, versus research in which POCBP may only be an incidental subject.

This document provides guidance on:

- Discussing and requiring **pregnancy prevention and/or testing** during active participation in a treatment protocol with known or unknown risks to pregnancy and/or fetuses.
- **Enrolling minors and discussing pregnancy risks, birth control, and/or requiring pregnancy testing** during active participation, or during a follow-up period, in a treatment protocol with known or unknown risks to pregnancy and/or fetuses.
- **Guidance on data collection or conducting interventions**, for participants that become pregnant during a study.
- **Guidance on data collection or interventions for a partner of a participant** that becomes pregnant while the partner is receiving an investigational new drug with unknown or known risks to pregnancy and/or fetuses.

Regulatory Citations

The following regulations and definitions form the foundation for the discussion and guidance in this document.

DHHS 45 CFR 46.102(e(1)):
Human subject means a living individual about whom an investigator conducting research obtains
(1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

DHHS 45 CFR 46.102(l):
Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

(4) ***Private information*** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

(5) ***Identifiable private information*** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Minimal Risk refers to risk that is no greater than the risks healthy adults encounter in daily life or during the performance of routine physical or psychological examinations or tests. For purposes of expedited review and relevant consent waivers in minimal risk studies, the standard for pregnant women is the same as for all adults.

FDA 21 CFR 50:
Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

DHHS 45 CFR 46 Subpart B: applies to research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates.

Criteria for Approval -
DHHS 45 CFR 46.111(2): Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

DHHS 45 CFR 46.111(6): When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

DHHS 45 CFR 46.111(7): When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

Discussion and Guidance

Research with an investigational treatment that will include POCBP requires attention to the additional health risks to pregnancy, the developing fetus, and/or exposure to breastfed infants. These protocols are to include steps to minimize such risks. In addition, the protocol should outline the following:

- The definition of “child-bearing potential” and the inclusion/exclusion of such participants.
- The circumstances when self-report of pregnancy status is sufficient, or whether clinical pregnancy testing is required. When clinical pregnancy testing is required, the protocol must include the type of testing that is indicated, the frequency and schedule for testing, and an explanation of when a validation/repeat test may be necessary, including who will pay for the test(s).
- The protocol should also include the procedures for disclosing the test results to participants.
- If the research is explicitly excluding pregnancy, the protocol must describe the risks that require exclusion, or state that the knowledge of the risks is so limited that pregnancy at the time of enrollment must be excluded.
- The plan to monitor and report pregnancies, any adverse outcome for the child/fetus, or adverse events suspected in infants following exposure to breast milk to the appropriate entities (IRB, sponsor, FDA, etc.) as applicable.

Often, participants are required to adhere to specified birth control measures and the number and methods may vary depending on the relative risks to the participant, the fetus, the participant’s partner and/or potential future pregnancy.

When a protocol includes the administration of an agent with known teratogenicity (e.g. thalidomide, chemotherapeutic agents or other anti-cancer agents, radiation, and others), the IRB will evaluate the timing and frequency of pregnancy testing to ensure safety of participants. The SH IRB may require that enrolled POCBP must have a negative pregnancy test (urine or serum) confirmed prior to each study drug administration. When an investigational agent has unknown risks, investigators are advised to ensure that POCBP have a negative pregnancy test at the time of enrollment and be assessed for potential pregnancy at the time of administration of the agent, as a minimum requirement. In both scenarios, it is recommended that participants agree to use reliable and highly effective methods of birth control.

Reliable and highly effective methods of birth control include: two forms of barrier contraception (e.g. condoms and foam; condoms and diaphragm); long-acting reversible contraception (e.g. subdermal contraceptive implant, intrauterine device, contraceptive injections), and oral contraceptive pills. In addition to discussing appropriate methods of contraception, it may be appropriate for the investigator to discuss reproductive options such as the banking of sperm or ova. If this discussion is to be included in the consent forms, then the investigator should address the advisability, availability, potential outcomes (to the extent the investigator is knowledgeable), and the associated costs.

Informed Consent Considerations for Treatment Studies with Known or Unknown Risks:

The consent form is to include the description of any known risks to the participant or to the embryo or fetus if the participant is or becomes pregnant. If the risks to the embryo, fetus, or pregnant person are unknown, the consent form is to include a statement of the unknown risks. The requirements of pregnancy testing and acceptable birth control methods are also to be described. The consent form must also discuss the study-specific reproductive harm(s) and the steps to minimize the harm. The consent should be written to address concerns appropriate to all populations involved.

When Pregnancy Occurs:

If a participant becomes pregnant during participation, the protocol and consent forms must describe the following:

- if the participant may remain in the study or is required to stop treatment;
- what follow-up information will be provided to the participant (e.g. counseling or referral to specific providers);
- the data to be collected about the pregnancy or outcome; and
- any additional short-term, or long-term, follow-up procedures or testing that will occur as a result of the pregnancy.

If the pregnancy occurs in the *partner* of a participant, the investigator or sponsor may wish to follow and collect data regarding the pregnancy and outcome (or follow the health of the infant).

The state of being pregnant is protected health information (PHI) of the partner, and information regarding the health of the infant is PHI. If an investigator or sponsor collects PHI of the pregnant partner or infant, for ***the purposes of research***, informed consent and HIPAA Authorization must be obtained prior to collection of this information. The investigator or the sponsor may not collect or record PHI regarding the partner's pregnancy or the health of the infant until the partner (or appropriate Legally Authorized Representative (LAR)) has given permission and signed the consent/HIPAA authorization form. The submission of the consent/HIPAA Authorization for this purpose may be submitted at the time of Initial submission or via a Modification at a later date.

When PHI is planned to be collected from a pregnant *partner* for research purposes, the investigator must outline in the protocol the purpose for the data collection (e.g. investigation of reproductive risks related to the study treatment, etc.), what specific data will be accessed and collected, the length of time data will be collected (e.g. outcome of the pregnancy only, infant health at 3 months, etc.). If the pregnant partner or LAR declines permission to obtain this information, the PHI may not be collected.

The SH IRB may be consulted in advance to determine if the purpose of the collection of PHI from a pregnant partner or partner's infant/child meets the definition of research. When there is planned inclusion of a pregnant person, including the additional collection of PHI from a pregnant partner for *the purpose of research*, the SH IRB will apply the regulatory standards of 45 CFR 46 Subpart B; 21 CFR Part 50, Subpart B as applicable.

Per FDA regulations (21 CFR Part 50), if the investigator or sponsor requests the collection of information from a pregnant partner or infant/child, *for safety monitoring only*, the pregnant partner/child may not meet the FDA definition of a human subject, and the collection or use of this data may not be a clinical investigation. However, the collection of PHI from the medical record requires the authorization from the pregnant partner/parent of a child prior to collection. If the IRB determines that the collection of the needed information is a not clinical investigation, a HIPAA Authorization form may still need to signed prior to collection of the PHI. If the sponsor has provided a general HIPAA Authorization to be used, this must be submitted to the SH IRB for review as the SH IRB also serves as the Privacy Board for research.

Special Considerations for Pregnant Minors in Research:

Under federal regulations, "children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of jurisdiction in which the research will be conducted. Per Michigan Law, when a child becomes pregnant, they are no longer considered a "child" and are considered an "emancipated minor". An emancipated minor may consent for themselves to receive treatment related to prenatal or pregnancy (except pregnancy termination) care. Per Spectrum Health Policy, *a minor may consent to enroll in a treatment protocol* that is related to prenatal care and/or their pregnancy, without requiring parental/LAR permission.

When an investigator is including minors in a treatment study with known or unknown risks to pregnancy, the fetus, or future pregnancy, the protocol must outline specific, additional protections, for these minors that may become pregnant. This includes special considerations regarding *the timing and nature of discussing required birth control and pregnancy testing* with the minor and/or parent/LAR. The Adolescent Assent form is to include these risks and the precautions required. The adequacy of the discussion of birth control and pregnancy testing will be reviewed by the SH IRB to ensure the rights and welfare of minors are protected.

In addition, the investigator is to outline in the protocol what steps/procedures will occur if a minor becomes pregnant while participating in the treatment study. It is advisable that the investigator *describe how and when a minor will be informed* of this pregnancy; including when/if results will be shared with a parent/LAR. For children <12 years of age, pregnancy test results are to be disclosed to the parent/LAR per Michigan Law.

For children ≥12 years of age, the investigator must determine if they will disclose this information to a minor and seek permission prior to informing a parent/LAR. This information should be explained to the parent and minor at the time of consent or prior to pregnancy testing. There may be situations in which the pregnancy of the participant presents health risks or there is suspected abuse and the pregnancy status may be disclosed without the minor's permission to a parent, LAR or other authorities.

If the investigator will not inform a parent/guardian of a pregnancy, then the investigator is required to discuss this with the minor explaining that the parent/LAR may realize this status on their own (e.g. due to removal from the study). The investigator must also inform the SH IRB if disclosure of this information places the minor at an increased risk.

Reporting Pregnancies:

Pregnancy is not considered an adverse event or a serious adverse event. However, this event may meet the criteria of an unanticipated problem that involves an increased risk to the participant, or a major protocol deviation/violation. The protocol must outline the procedures for monitoring for pregnancies and the outcome based on the known and unknown risks related to the study treatment (i.e. will the pregnancy be followed until termination or to term to ensure absence of congenital anomaly or birth defect).

Pregnancies occurring in research that is determined to be more than minimal risk *are to be reported* via the Reportable New Information (RNI) x-Form within five business days of investigator knowledge of the event. For research that is determined to be minimal risk, investigators are to follow the reporting policy outlined in the RNI Guidance document. The SH IRB will review and determine if the pregnancy meets the criteria as an Unanticipated Problem. The investigator is to follow all reporting criteria from the Sponsor, Lead Site, and/or FDA for these events.

Conclusions

- Enrolling participants in investigational treatment protocols with known or unknown risks to pregnancy, a developing fetus, and/or future pregnancy requires the inclusion of special precautions in order to protect participants.
- The protocol and consent form(s) must clearly explain all known and unknown pregnancy/fetal risks and the methods of birth control that will be required to prevent pregnancy during participation.
- The consent form(s) must also include what will occur if a participant, or a partner of a participant, becomes pregnant.
- If a pregnancy occurs, additional information may be collected related to the health and outcome of the pregnancy. This information is PHI and consent and/or HIPAA Authorization may be required prior to the collection and use/disclosure. The SH IRB can assist with determining which form(s) are to be completed, when necessary.
- When minors are enrolled in a treatment protocol that includes the requirement of birth control and/or pregnancy testing, the investigator is to include in the protocol plans for the disclosure of pregnancy results to both the minor and parent/LAR including when this information may be withheld due to placing the minor at additional risk (e.g. in cases of abuse).
- Report pregnancies that occur during research that presents more than minimal risk to participants. Consult the Guidance on Reportable New Information to determine when pregnancy is to be reported for minimal-risk studies.

Contact the SH IRB for more information: irbassist@spectrumhealth.org