IRB Review of Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Regulatory Framework and Requirements: Research involving pregnant subjects, fetuses, or neonates must comply with Subpart B: Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research under 45 CFR 46.

Definition of Pregnancy: Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery. (45 CFR 46.202(f))

Research Inclusion/Exclusion Scenarios[1]

Pregnant Subjects Are Included:
• The Principal Investigator (PI) must justify the inclusion of pregnant subjects in the protocol.
Protocol Does Not Address Inclusion/Exclusion of Pregnant Subjects:
• If pregnancy occurs during a study, justification for continued inclusion of the pregnant subject must be provided via study modification. • In minimal-risk studies, pregnancy may not need to be specifically addressed unless research procedures require pregnancy testing. In such cases, the protocol should indicate that pregnancy testing will be done and results must be negative.
Pregnant Subjects Excluded:
• Justification for exclusion should consider study risks and scientific validity. • If a participant becomes pregnant, a protocol modification must be submitted for IRB approval to justify their continued participation.
FDA-Regulated Studies:
• Pregnant subjects are generally excluded from drug development trials but may be included based on ethical and scientific considerations. • Follow-up of pregnant participants or their partners may be required. (See IRB Responsibilities section.) • See the draft guidance for industry: Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials.

Required Protocol and Consent Documentation

Protocol Documentation	• If the research enrolls pregnant women, fetuses or neonates, the study must satisfy all of the requirements of 45 CR 46 subpart B. Refer to NIH HRPP Policy 400, *Research Involving Pregnant Women, Human Fetuses, and Neonates* to ensure sufficient information is provided to allow this study meets Subpart B determination criteria. • PI should define individuals who can become pregnant, if applicable. • If eligibility criteria exclude pregnant and/or lactating women, a justification for the exclusion based on scientific or safety concerns should be explicitly stated. • If the study does not intentionally enroll pregnant women, but it is possible a participant may become pregnant, if the researcher intends to keep the participant on the study (pregnancy is not an off-study criterion), then the protocol must provide sufficient justification and information for the IRB to determine that all of the requirements of Subpart B are met. • Protocol should specify which research procedures are applicable to pregnant participants. • Include pregnancy testing details when relevant. (e.g., prior to CT/MRI scan)
Consent Documentation	• Include a brief statement in the consent describing known, suspected, or unknown risks to a developing fetus or breastfeeding infant. • Provide a brief statement and explanation in the consent if pregnancy is being excluded for scientific reasons. • Standard of care practices such as pregnancy testing before a CT scan do not need to be included in the consent, however, a description does need to be included if the timing or method of pregnancy testing differs from standard of care.

[1] See NIH IRP Guideline for Inclusion/Exclusion of Pregnant People and Information About Pregnancy Testing on the IRBO website under Policy 400 for more details.

IRB Responsibilities When Reviewing Protocols That Involve Pregnant Participants or Fetuses

- The IRB must ensure that regulatory protections from both Subparts A and B are met.
- IRB decides if there is prospect of direct benefit (PDB) and risk level to determine if approvable under Subpart B.
- Research that has the **PDB to the pregnant woman and/or the fetus** is generally approvable even if greater than minimal risk when the other Subpart B requirements are also met.
- When there is **no PDB** to the mother or fetus:
  - The IRB may may only approve the research if the risk is **no greater than minimal**, and the *purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means*.
  - The IRB must review the justification provided in the protocol and determine that the aim of gaining such knowledge cannot be achieved by enrolling only nonpregnant participants.
- Research involving pregnant participants that is **greater than minimal risk with no PDB** to the pregnant participant or the fetus cannot be approved by the IRB.
- For studies **greater than minimal risk with no PDB** that do not enroll pregnant women, the IRB should ensure the protocol addresses what will happen if participants or their partners become pregnant during the study:
  - The protocol should specify the timepoints at which pregnancy testing is required.
  - The protocol should indicate if pregnancy is an off-treatment criterion.
- If participants or their partners become pregnant during the course of the study and collecting pregnancy outcome data is required (e.g. for FDA regulated research), a new cohort including pregnant participants/partners must be added to the protocol, and members of this cohort must provide consent for follow-up of pregnancy outcome. Alternatively, the protocol can include a plan to ask the pregnant subject/partner to enroll in the *NIH Intramural Research Program's Pregnancy Registry Protocol for Subjects and Their Partners* (IRB protocol #000268).

Regulatory Conditions for Approval of Research Involving Pregnant Women or Fetuses (45 CFR 46.204)

a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
c) Any risk is the least possible for achieving the objectives of the research.
d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A.
e) If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
g) For children who are pregnant, assent and permission are obtained in accord with the provisions of Subpart D.
h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
j) Individuals engaged in the research will have no part in determining the viability of a neonate.