Research Involving Pregnant Women, Fetuses, and Neonates

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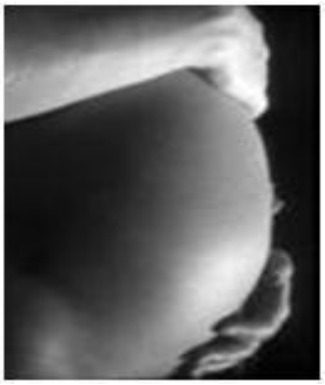
Introduction

Women as Subjects of Research

Historically, in order to avoid harm to a developing fetus in an unsuspected pregnancy, women of childbearing potential were excluded from biomedical research. For example, the U.S. Food and Drug Administration's (FDA) 1977 guidelines excluded women of childbearing potential from early phase drug trials. In the late 1980s and early 1990s, recognizing that as a consequence of this "protection," women were being denied the benefits of research, women's groups began advocating strongly for expanded access. In 1988, the FDA issued guidelines that called for safety and efficacy profiles for women as part of all new drug applications, and in 1993, eliminated restrictions on women of childbearing potential participating in all phases of drug development. In 1994, the National Institutes of Health (NIH) issued guidelines requiring the inclusion of women in research. The NIH concluded that the only justification for exclusion of non-pregnant women of childbearing potential was compelling evidence that inclusion would be inappropriate with respect to the subjects' health, or to the research's purpose.

Pregnant Women and Fetuses as Subjects of Research



Since the 1930s, biomedical researchers in the U.S. have used ex utero fetal tissue as an object of experimentation, including production and testing of vaccines, propagation of human viruses, and testing of biological products. The 1954 Nobel Prize for Medicine was awarded to researchers who utilized human fetal kidney tissue cell lines to grow poliovirus in culture. In the early 1970s, however, the great societal debate over Roe v. Wade prompted Congress to charge the newly established National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to report on research using the human fetus.

The National Commission's report, submitted in July 1975, formed the basis for the U.S. Department of Health and Human Services (HHS) regulations at 45 CFR 46, Subpart B - Additional Protections Pertaining to Research, Development, and Related Activities Involving

Fetuses, Pregnant Women, and Human In Vitro Fertilization. In 2001, HHS issued modifications to Subpart B, now entitled "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research."

Learning Objectives

By the end of this module, you should be able to:

- Describe the types of research permitted with women under 45 CFR 46, Subpart B.
- Identify from whom consent is needed when conducting research with fetuses under 45 CFR 46, Subpart B.
- Discuss the requirements for conducting research with neonates of uncertain viability under 45 CFR 46, Subpart B.

Research Involving Pregnant Women or Fetuses

45 CFR 46, Subpart B generally allows research involving pregnant women or fetuses only if appropriate studies on animals and non-pregnant individuals have been completed. In addition, if the research is not intended to meet the health needs of the mother or the fetus, the risk to the fetus must be minimal. 45 CFR 46, Subpart B gives no specific guidance regarding the definition of "minimal risk" in this context. In any case, the risk to the fetus must be minimized to the greatest extent possible.

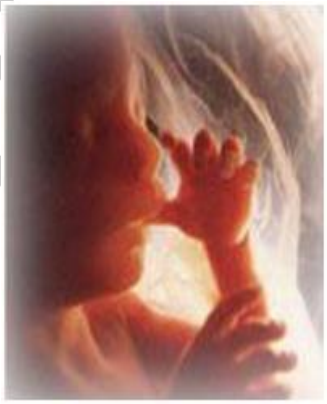
	Benefit to Mother or Fetus	**No Benefit**
Minimal Risk	Allowed	Allowed if purpose is development of important biomedical knowledge
Greater Than Minimal Risk	Allowed if risk to fetus is the least possible	Not Allowed

To minimize the possibility that involvement in research will influence a mother's decision to terminate a pregnancy, 45 CFR 46, Subpart B also excludes researchers from any decisions as to the timing, methods, or procedures used to terminate a pregnancy, or determinations on the viability of the fetus at the termination of the pregnancy. Research involving pregnant women and fetuses may be conducted only if consent is obtained from the mother, or from both parents, after she/they have been fully informed regarding the possible affect of the research on the fetus. If the research has the prospect of direct benefit to the mother or has minimal risk to the fetus, only the mother's consent is needed. If the research has the prospect of direct benefit only to the fetus then consent of both parents is required. The other parent's informed consent also does not need to be secured if his/her identity or whereabouts cannot reasonably be ascertained, if he/she is not reasonably available, or the pregnancy resulted from rape or incest.

Who Needs to Consent	
Mother Only	**Both Parents**
Research poses no direct benefit and only minimal risk to mother or fetus (45 CFR 46.204 [b])	Research has no prospect of direct benefit for mother, but does have prospect of direct benefit for the fetus only (45 CFR 46.204[e])
Research has prospect of direct benefit for mother only and minimal risk to the fetus (45 CFR 46.204[b])	
Research has prospect of direct benefit for both mother and fetus (45 CFR 46.204[b])	

Details on the Requirement of Maternal Consent.

Research Involving Neonates



After a fetus is delivered, it is termed a neonate (newborn). Neonates of uncertain viability or non-viable neonates may also be subjects of research regulated by 45 CFR 46, Subpart B. Viability is defined as the ability of the fetus to survive, given the benefit of available medical therapy, to the point of independently maintaining heart beat and respiration. This definition makes it clear that viability is a moving target.

Neonates of uncertain viability may be involved in research only if there is no added risk to the fetus, or the research's purpose is to enhance the possibility of survival of the particular fetus to the point of viability. Consent of a legally competent parent, or either parent's legally authorized representative (LAR) is needed.

If a fetus is determined to be non-viable after delivery, it may only be involved in research if:

- The fetus's vital functions will not be artificially maintained;
- No experimental activities, which of themselves would terminate the heartbeat or respiration of the fetus, will be employed;
- There will be no additional risk to the neonate; and
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means. Consent of a legally competent parent, or parent's LAR, is needed.

If a fetus is determined to be viable after delivery, it is a child. Research involving that viable newborn is governed by 45 CFR 46, Subpart D - Additional Protections for Children Involved as Subjects in Research.

Research Involving the Dead Fetus, Fetal Material, or the Placenta

45 CFR 46, Subpart B does not directly regulate research involving the dead fetus, stating only that these research activities shall be conducted in accordance with any applicable federal, state, or local laws. In most states, the use of tissue from dead fetuses for research purposes would fall under the Uniform Anatomical Gift Act (UAGA), which requires consent of both parents. However, some states specifically ban research that involves aborted fetuses, or their organs, tissues, or remains.

Research involving fetal material for transplantation, and utilizing embryos produced by *in vitro* fertilization for the generation of human embryonic stem cell lines have been subject to additional restrictions.

Vulnerable Subjects - Research Involving Pregnant Women, Human Fetuses, and Neonates

PART 1

A researcher submits a NIH-funded study to the Institutional Review Board (IRB) for review. The study proposes to evaluate a risk scoring system to help predict which women with pre-eclampsia (a condition in pregnant women characterized by high blood pressure, and protein in the urine) will progress to eclampsia (characterized by seizures, organ failure, and high risk of death), or otherwise have poor outcome. The system will use both clinically obtained blood tests and a small amount of extra blood for research tests, as well as pre-natal history, to classify women as low or high risk. The researcher will then monitor the outcomes of the pregnancies, and correlate the outcome with the "risk category."

Pregnant women 20 to 40 years of age with pre-eclampsia are eligible. All subjects are otherwise healthy and competent.

The IRB determined that there was no prospect of direct benefit to the pregnant woman. It further decides that there is minimal risk to the pregnant woman or fetus, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.

- Who needs to give consent for the pregnant woman (and the fetus) to participate in this research?

  According to 45 CFR 46.204(d) (Protection of Human Subjects 2009):

  > If the research holds out…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 of this part.

  Because there is no prospect of direct benefit (and the research is minimal risk and intended to develop important biomedical knowledge), only the consent of the pregnant woman is needed. Consent from the other parent is not required.

PART 2

Based on preliminary data obtained from the previous study, the researcher decides that a blood sample from the fetus while still in-utero (in the womb) could refine the scoring system. The process of in-utero blood sampling is considered greater than minimal risk to the fetus.

- Is the research approvable under 45 CFR 46.204?

  No. 45 CFR 46.204 (Protection of Human Subjects 2009) states that for research to be approvable:

  > 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.

  Because the in-utero fetal blood sampling is greater than minimal risk without prospect of direct benefit to the pregnant woman or the fetus, the research is not approvable under 45 CFR 46.204. The research might still be approvable, per 45 CFR 46.207 (Protection of Human Subjects 2009), if it "presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates."

PART 3

To make his latest project approvable, the researcher amends the research plan to obtain cells by amniocentesis rather than fetal blood sampling. He will restrict enrollment to older pregnant women who would be getting amniocentesis for clinical indication, or to pregnant women who would be at high risk for having a fetus with trisomy 21 and for whom an amniocentesis would provide information valuable to them.

The IRB now believes there is potential for direct benefit to the pregnant women, though greater than minimal risk to the fetuses.

- Is the research approvable under Subpart B?

  In order to be approvable under Subpart 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." Because the IRB believes that the amniocentesis carries direct benefit to the woman, then 45 CFR 46.204(b) is satisfied. The research is potentially approvable (provided the other conditions of Subpart B are met).

- If approvable under Subpart B, who must provide consent?

  Further, per Subpart B "If the research holds out the prospect of direct benefit to the pregnant woman [or] the prospect of a direct benefit both to the pregnant woman and the fetus … her consent is obtained in accord with the informed consent provisions of subpart A." The consent of the pregnant woman alone is necessary.

PART 4

The same researcher now proposes to develop cell lines from tissues obtained from miscarried (deceased) fetuses from mothers with eclampsia. He will also obtain protected health information (PHI) with identifiers from the mothers of the dead fetuses, so he can potentially contact them in the future to obtain blood for future research purposes, as well as to capture basic information that might be important to future research.

- Is this human subjects research?

  Because the researcher will obtain identifiable information from the mother, she is a human subject and this is human subjects research.

- If the study is considered human subjects research, is it subject to 45 CFR 46, Subpart B?

The research involving the fetal tissue is not subject to 45 CFR 46, Subpart B (Protection of Human Subjects 2009) because:

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

Nonetheless, obtaining identifiable information from the mother means her participation is subject to 45 CFR 46, Subpart A.

It is important to remember that, though the research involving the fetal tissue may not be subject to Subpart B, it is subject to any applicable federal, state, or local laws and regulations regarding such activities. Therefore, there may still be restrictions on the researcher (and the research). In most states, the use of tissue from dead fetuses for research purposes would fall under the UAGA, which requires consent of both parents. However, some states specifically ban research that involves aborted fetuses, or their organs, tissues, or remains.

Summary

Pregnant women, as a population in research, are protected through regulatory safeguards. The regulations provide a framework to understand when and how to include the population in research, not just to exclude them entirely. IRBs and researchers should understand the regulations in order to ethically include pregnant women in research.

Reference

- Protection of Human Subjects, 45 CFR § 46 (2009).

Additional Resources

- National Institutes of Health (NIH). 1994. "NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research." Accessed March 16, 2016.
- U.S. Department of Health and Human Services (HHS) and U.S. Food and Drug Administration (FDA). 1993. "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." Accessed March 16, 2016.

- U.S. Food and Drug Administration (FDA). 1988. "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application." Accessed March 16, 2016.
- U.S. Food and Drug Administration (FDA). 1997. "Guidance for Industry: General Considerations for the Clinical Evaluation of Drugs." Accessed August 18, 2016.
- U.S. Food and Drug Administration (FDA). 2018. "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials." Accessed April 12, 2018.

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