SOP 7.03 - Vulnerable Subjects: Pregnant Women, Human Fetuses and Neonates

1. Objective

The purpose of this SOP is to describe considerations for conducting research with women who are or may become pregnant, or research that is directed towards a fetus or neonate. The IRB will consider approval of research involving these populations when the research satisfies the conditions of 45 CFR 46, Subpart B and Subpart D as explained in this policy.

2. General Description

Federal regulation 45 CFR 46 Subpart B requires that principal investigators and the IRB shall be sensitive and apply special conceptual and regulatory protections to research involving pregnant women, human fetuses and neonates.

Definitions

Fetus **-** means the product of conception from implantation until delivery.

Neonate - means a newborn.

Nonviable neonate - means a neonate after delivery that, although living, is not viable.

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.

Viable **-** as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements for research involving children.

3. Roles & Responsibilities

Execution of SOP: Principal Investigators (PI)/Study Personnel (SP), IRB Chair, IRB, Office of Research Integrity – Human Subjects (ORI-HS) Staff.

IRB
The IRB will carefully review the inclusion of pregnant women, human fetuses, and/or neonates as research subjects to ensure that additional protections are in place.

Investigators
Investigators shall acknowledge and be sensitive to the vulnerability of subjects who are pregnant or newborn especially within the unique times of labor and delivery. Investigators shall also take into account that the health and wellbeing of the mother, the fetus and/or the newborn should take priority over the goals of any research study. Investigators shall ensure the highest possible standards in the conduct of research involving these populations as subjects.

4. Procedures

Research involving pregnant women or women of childbearing potential may be considered for approval by the IRB once the following determinations are made and documented:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for the risk/benefit assessment for pregnant women and fetuses;
2. When the research has the potential of directly benefiting the woman or the fetus, a greater than minimal risk to the fetus is acceptable. If the research does not hold the prospect of directly benefiting the woman or fetus, then the research is allowed if 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;
3. Any risk is the least possible for achieving the objectives of the research;
4. The pregnant woman's consent is sufficient when there is the prospect of direct benefit for the pregnant woman, the pregnant woman and the fetus, or when there is no prospect of benefit for the woman or the fetus but the 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,
5. When the research has the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father of the fetus is required, except that the father's consent is not required if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or the pregnancy resulted from rape or incest;
6. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. In the case of pregnant females who are themselves minors (under age 18), assent and permission are obtained in accordance with SOP 6.02 and 7.01;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

In conducting an IRB-approved research study involving pregnant women and fetuses, investigators should carefully and sensitively consider the process for obtaining informed consent. Whenever practical and feasible, information about the study should be made available prior to labor. If the patient must be approached during labor, permission should be sought first from the patient's obstetric care provider and the patient's primary nurse should be involved in discussions regarding the appropriateness of such an approach. If the obstetric care provider and/or the primary nurse

believe that the patient may not comprehend a research protocol, the patient should not be approached for research participation. Investigators should also delay approaching patients for research participation if the patient's capacity for informed consent is impaired by medications.

Non-clinical Biomedical and Behavioral Research Involving Pregnant Women to which Subpart B may not apply

The IRB recognizes that some types of research that could be conducted with pregnant women do not fit specifically within the regulatory requirements for approval. For example, the additional safeguards required under Subpart B may not directly apply to minimal risk research involving interviews, surveys, oral histories and other non-clinical biomedical, behavioral and educational research.

The IRB also recognizes that some research that targets a wide population may coincidentally encounter pregnant women as potential research participants, yet does not present additional risks to participants who are or may become pregnant. Investigators and the IRB will nonetheless consider the research in light of the inclusion of pregnant women, and the IRB will use the criteria as a framework in determining approval.

Coincidental Pregnancy

There are circumstances in which pregnancy is coincidental to participant selection and safeguards may need to be in place if a subject becomes pregnant. In these circumstances, the IRB shall determine such matters as to whether or not:

- Participants should be advised on the risks of participation in the study
- Participants should be advised to avoid pregnancy or nursing during or following participation in the study
- 3Participants should be advised to notify the principal investigator immediately should they become pregnant
- Participants should avoid causing a pregnancy during or following participation in the study and whether the participant should notify the principal investigator should the participant cause a pregnancy
- Pregnant women should specifically be excluded from the study or whether specified methods of contraception should be required during or following participation in the research

IRB Approval of Research Involving Neonates

Research involving neonates of uncertain viability and nonviable newborns may be approved by the IRB once the following determinations are made and the findings are documented:

- Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
- Each individual providing consent, as discussed below, is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- Individuals engaged in the research will have no part in determining the viability of a neonate.
- The requirements below have been met, as applicable.

Neonates of Uncertain Viability
Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

The IRB determines that:

- The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or
- The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
- The legally effective informed consent of either parent of the neonate, or if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the IRB may approve the substitution of the informed consent of either parent's surrogate or legally authorized representative being obtained except that the consent of the father or his surrogate or legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Note: Surrogate consent processes must be consistent with all applicable State laws

Nonviable Neonates
After delivery the nonviable neonate may not be involved in research unless all of the following additional conditions are met:

- Vital functions of the neonate will not be artificially maintained;
- The research will not terminate the heartbeat or respiration of the neonate;
- There will be no added risk to the neonate resulting from the research;
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
- The legally effective informed consent of both parents of the neonate is obtained in accord with SOP 6.01, except that the waiver and alteration provisions do not apply.

Note: If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet these requirements.

Viable Neonates
A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of SOPs 6.01 and 6.02.

IRB Approval of Research Involving, after Delivery, the Placenta, the Dead Fetus or Fetal Material
Research involving the placenta, dead fetus or macerated fetal material, or cells, tissue, or organs excised from a dead fetus, if information associated with this material is recorded for research purposes in a manner that living individuals (e.g., parents, siblings) can be identified, directly or through identifiers linked to those individuals, requires IRB review and approval prior to imitation of

such activities. If such identification is possible, then those individuals are research subjects and all pertinent federal regulations involving human research subjects are applicable. (45 CFR 46.206). The research shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

Federal Laws Governing Research on Transplantation of Fetal Tissue
Federal law which may apply to research involving fetal tissue requires that, for research carried out on human fetal tissue, the woman providing the tissue makes a signed statement declaring that:

- the woman donates the fetal tissue for use in research;
- the donation is made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue; and
- the woman has not been informed of the identity of any such individuals. Furthermore, the tissue may be used only if the individual with the principal responsibility for conducting the research (the principal investigator) makes a signed statement declaring that he/she: is aware that:
    - the tissue is human fetal tissue; other tissue may have been obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth; and
    - the tissue was donated for research purposes

- has provided such information to other individuals with responsibilities regarding the research;
- will require, prior to obtaining the consent of an individual to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of such information by such recipient; and has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purposes of the research.

Non-embryonic Stem Cell Research
Researchers proposing to conduct research with non-embryonic stem cells must comply with all requirements of federal and state laws regarding the conduct of human non-embryonic stem cell research.

Research involving human stem cells is subject to Nevada laws governing use of non-embryonic stem cells (AKA "somatic" or "adult" stem cells) (NRS 629 Non-embryonic Cells). At the present time, there are no Nevada statutes for the use of embryonic stem cells. University and affiliate investigators wishing to conduct research with human stem cells are advised to obtain legal counsel.

Research Not Otherwise Approvable
Research that does not meet the aforementioned approval criteria must be approved by the Secretary of Health and Human Services (45 CFR 46.207). If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates, and the research is not approvable under the above provisions, then the research must be sent to DHHS OHRP for the review and approval by the Secretary of Health and Human Services.

Special Situations/Exceptions

Pregnant Children

According to Nevada law, minors are persons under the age of eighteen (NRS 159.023). The general rule is that a person may consent for his or her own medical care at the age of eighteen. However, certain statutes and case law provide minors with majority status in some circumstances, for example: emancipated minor (NRS 129.030). The IRB will consider on a case-by-case basis the appropriateness of involving pregnant minor females in research, and approve such research only after careful deliberation with University counsel and pediatric and obstetric specialists on the board (or speak with consultants if IRB members with the requisite expertise are not available for discussion). In other jurisdictions, investigators should consult local law.

Women of Childbearing Potential: Reproductive Risks
National Institutes of Health policy requires the inclusion of women in research study populations so that research findings can be of benefit to all persons at risk of the disease, disorder, or condition under study. Where research involves potential risk sufficient to justify requiring that pregnant women either be specifically excluded or studied separately, prospective study participants should be tested for pregnancy and warned about possible and/or unknown reproductive or lactation risks from study treatments. Investigators must discuss these risks and the steps taken to minimize them in both the consent form and in the protocol application. Subjects should be advised to notify the investigator immediately should they become pregnant.

Studies to Develop or Evaluate Methods of Enhancing Conception or Contraception
These studies are closely related to research involving pregnant women and raise some of the same concerns. There are no special regulations for this category of research, but special IRB attention is needed. IRBs should ensure that there is an adequate explanation of the risks, benefits, reversibility, and alternatives; that backup protection against unintended pregnancy is provided when appropriate; and that the possibility of failure (and options available for dealing with unintended pregnancies) are satisfactorily described.

In-Vitro Fertilization
While in vitro fertilization (IVF) research is not currently supported by federal funding or protected by federal law, some investigators may be involved in privately-funded research on IVF as a treatment for infertility or other problems. In such cases, investigators are still required to seek IRB review and approval before initiating such human research. A critical consideration in IVF research is assuring that, where gamete donors are known, an agreement exists between donors and recipients. Additionally, investigators should be aware that embryos that are being studied at temperatures that allow them to develop cannot be studied beyond 14 days old.

5. References

Adapted from University of Nevada, Reno Policy II4A-B:
http://www.unr.edu/Documents/research/RIO/manual/II4A-B_PO_ParticipationPregnantWomenandFetuses_022712.pdf

45 CFR 46 Subpart B

Institutional Review Board Management and Function, Bankert & Amdur – Chapter 9-6

OHRP Institutional Review Board Guidebook, Chapter VI - Special Classes of Subjects

NRS 629 Non-embryonic Cells
NRS 159.023
NRS 129.030
PUBLIC LAW 103-43; JUNE 10, 1993: RESEARCH ON TRANSPLANTATION OF FETAL TISSUE (http://www.hhs.gov/ohrp/policy/publiclaw103-43.htm.html)

US DHHS OHRR [now OHRP] Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles, March 19, 2002

The American Society for Reproductive Medicine (http://www.asrm.org/)