12.1 THE PROTECTION OF VULNERABLE POPULATIONS IN HUMAN SUBJECTS RESEARCH

All human subjects warrant protection from the risks of participation in research. However, certain populations of subjects, those who are termed "vulnerable," require additional, special protection. Federal regulations indicate, "The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons."

Special subparts have been included in the Code of Federal Regulations (CFR) to address special protections for three populations in particular - pregnant women, human fetuses and neonates (45 CFR 46 Subpart B), prisoners (45 CFR 46 Subpart C), and children (45 CFR 46 Subpart D and 21 CFR 50 Subpart D). However, there exist other classes of subjects who may be subject to other vulnerabilities, for example, HIV positive people,that must be considered by the IRB during the review of a protocol.

12.2 PROTECTIONS FOR PREGNANT WOMEN, HUMAN FETUSES, AND NEONATES

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

Definitions:
Pregnancy encompasses the period from implantation until delivery.

Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means. 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.

Fetus means the product of conception from implantation until delivery. *Dead fetus* means a fetus that does not exhibit a heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord.

Neonate means a newborn (first four weeks of life, i.e. less than 28 days of age).

Viable neonates are regulated under Subpart D of 45 CFR 46 (research involving children). 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.

A. Inclusion of Pregnant Women or Women of Childbearing Potential in Research

In accordance with the principle of justice described in the Belmont Report, pregnant women must not be excluded from research without appropriate medical or scientific justification. During the course of a clinical study, pregnant women or women of childbearing potential may be encountered coincidentally as potential subjects. Alternatively, pregnant women and fetuses may be the target study population(s). Federal regulations do not distinguish between research in which pregnant women or fetuses are a target population, versus research in which pregnant women or fetuses may be only incidental subjects.

i. Conducting research where pregnant women are not the target population

a. If the research is targeting a wide population, which includes women of childbearing potential, there is a possibility of pregnancy and therefore a possibility of enrolling pregnant women.

b. The research protocol should define any conditions for inclusion or exclusion of pregnant women or women of childbearing potential who may be encountered during study enrollment.

c. For research that involves minimal risk, or no physical risks to subjects, and where pregnant women are not the target population but may be enrolled incidentally, the study consent forms need not include a statement that the research may involve currently unforeseeable risks to the pregnant women or fetus. Additionally, there are no requirements concerning the purpose of the research in regards to the inclusion of pregnant women.

    - In regards to pregnant women, "minimal risk" should be understood as risk not greater than the risks healthy adults have in common in daily life or encounter in common 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.[1]

d. The consent form for treatment and intervention studies, that are more than minimal risk, or includes physical risks, should describe any known risks to the subject or to the embryo or fetus if the subject is or becomes pregnant. If the risks to the embryo, fetus, or pregnant woman are not known because there is little experience of the treatment or intervention in pregnant women, the consent form should clearly say so.

i. Conducting research where pregnancy is an exclusion criteria

a. If the research is explicitly excluding pregnant women, the protocol must describe the risks that require exclusion, or state that the knowledge of the risks is so limited that pregnancy should not occur.

b. For research that poses a risk to either a pregnant women or a fetus, all non-pregnant and sexually active male subjects should be instructed on the methods to avoid pregnancy during and after the study, advised about pregnancy testing that may be required before and during the study, In addition, the consent form should clearly describe information about avoiding pregnancy and about pregnancy testing that may be required.

c. The following must be addressed in the protocol/research plan and consent forms when pregnancy is an exclusion criteria:

    - Definition of child-bearing potential
    - Circumstances when self-report of pregnancy status is adequate, specifically when there is no expected risk to a fetus
    - Whether a clinical test, as opposed to self-report, is indicated
    - The type of clinical test indicated

- When the test needs to be performed, whether it should be repeated, and how often
- Who will pay for the pregnancy test(s)
- How the results will be disclosed to the subject
- Required information in the consent form addressing notification of minors and their parents/guardian/LAR

d. The consent form must also discuss the study-specific reproductive harm(s) and the steps to minimize the harm. These harms may be unique to one gender or may be different for men and women involved in the study; the consent should be written to address concerns appropriate to all populations involved.

e. In addition to discussing appropriate methods of contraception and abstinence, 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 investigator should address the advisability, availability, potential outcomes (to the extent the investigator is knowledgeable), and the associated costs.

f. If pregnancy occurs, the protocol and consent documents should discuss what will happen if a subject, or the partner of a subject, becomes pregnant. Typically, the subject should contact the investigator, who can then discuss risks and provide counseling about additional steps to be taken. If the researchers, or sponsors of the research, want to monitor any offspring after birth, regardless if this is short term or long term, this should be discussed in the consent documents. This discussion should include what data is to be collected and for what purpose, whether the data will be identifiable, and how long the data will be stored. In some circumstances, the offspring may then be considered a research subject and thus, Subpart D (Additional Protections for Children Involved as Subjects in Research) may apply.

g. Some studies find it useful to provide special consent forms for subjects who become pregnant and wish to continue participation in the study. This special consent form should then discuss the risks to the pregnant women, the fetus, and the offspring, and any special additional precautions or follow-up for the pregnant women and offspring. If the subject consents to remain in the study during pregnancy, immediate notification to the IRB Chair of this decision is required. The study will then be required to undergo review and approval under Subpart B at the next convened meeting.

i. Conducting research with pregnant women as a target study population

a. If the research is conducting human subject's research with pregnant women (target study population) then Subpart B of the federal regulations (45 CFR 46) applies. Note: the FDA is not a signatory of 46 CFR 46.201 – 207 (Subpart B).

b. If the research is conducting research with pregnant women, the protocol must outline the risk assessment and justify the inclusion of both the pregnant women and the fetus. Appropriate precautions should be taken in research studies to

guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects of potential risk and the need for precautions.

c. If the research holds the promise of directly benefiting the woman or 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, the research is allowed if the risk to the fetus is not greater than minimal.

- In regards to fetuses, "minimal risk" should be understood as risk that is not greater than the fetal risks associated with the risks that healthy pregnant women ordinarily encounter in daily life and have in common with other healthy adults or the risks to the fetuses encounter during routine prenatal examinations or tests of healthy women and healthy fetuses.[1]

d. In addition, the risks to the pregnant woman are to be reasonable in relation to any anticipated benefits to the pregnant woman and fetus and the importance of the knowledge that may reasonably be expected to result.

e. Additional conditions and protections apply to obtaining informed consent from pregnant women, and their partners, if applicable under Subpart B. These are described below in section C.

B. Additional Protections for Research Involving Pregnant Women or Fetuses

The federal regulations (45 CFR 46.204) specify that pregnant women or fetuses may be involved in research if all of the following conditions are met:

i. 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 assessing potential risks to pregnant women and fetuses;

ii. Any risk is the least possible for achieving the objectives of the research;

a. 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

b. 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 (i.e. the inclusion of pregnant women in the research is necessary in order to obtain the data);

iii. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

iv. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy or decisions regarding the viability of a fetus

C. Requirements for Consent

Depending on the nature of research, consent from individuals other than the pregnant subject may be required.

i. Only the consent of the pregnant woman is required when the research:

   a. holds out the prospect of direct benefit to the pregnant woman; or

   b. holds out the prospect of a direct benefit both to the pregnant woman and the fetus; or

   c. holds out no prospect of benefit for the woman nor the fetus, but 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 mean (i.e. that the inclusion of pregnant women in the research is necessary in order to obtain the data).

ii. The consent of both the pregnant woman and the father of the fetus is required if the research holds out the prospect of direct benefit solely to the fetus. The requirement for obtaining the father's consent is waived if he is unable to consent because of unavailability, incompetence, or temporary incapacity or if the pregnancy resulted from rape or incest. If the pregnant woman is a competent adult and the father is a minor, his consent, along with the mother's, would be required for any experimental research that is of direct benefit solely to the fetus.

A number of women enter pregnancy with health problems or develop new ones during pregnancy. Some problems are affected positively or negatively by pregnancy; others are unaffected. A considerable amount of research is conducted on health problems that affect women during pregnancy (e.g., arthritis, hypertension, diabetes); despite standard therapy, deterioration of maternal health may also necessitate experimental treatment. In research undertaken to address the health problems of a pregnant woman, her needs generally take precedence over those of the fetus, except where the health benefit to the woman is minimal and risk to the fetus is high **(**45 CFR 46.207**)**. For example, if an experimental drug were considered necessary to improve a pregnant woman's condition, her consent alone would be sufficient to authorize its administration – even though it might have unknown or greater than minimal risk for the fetus.

Illinois law (Consent by Minors to Medical Procedures Act) allows a pregnant minor to consent (without prior parental permission) to medical care which is related to the prevention, clinical treatment, or termination of her pregnancy. Therefore, if a research study involves the provision of standard clinical care or treatment to pregnant women, minors may make a decision regarding their participation; the consent of the parent/guardian of the minor is not required.

If an investigator anticipates that pregnant minors may be recruited for participation, the investigator must detail how pregnant minors will be consented so that the IRB may specifically address this issue in its review.

D. Research Involving Either Neonates of Uncertain Viability and Nonviable Neonates

The federal regulations (45 CFR 46.205) specify that neonates of uncertain viability or nonviable neonates may be involved in research only if the following conditions are met:

i. Where appropriate, preclinical (animal) and clinical studies have been conducted and provide data for assessing potential risks to neonates;

ii. Each individual providing consent is fully informed regarding the reasonable foreseeable impact of the research on the neonate; and

iii. Individuals engaged in the research will have no part in determining the viability of a neonate.

Per CFR 46.202, a nonviable neonate is defined as a neonate after delivery that, although living is not viable.

E. Research Involving 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:

i. 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

ii. 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

iii. The legally effective informed consent of either parent of the neonate is obtained. However, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR must be obtained. The consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest. Please note that, under both Illinois law and federal regulations, minor parents have the same rights as any adult parent to consent to research involving their children.

The IRB's role is to ensure that individuals engaged in the research will have no part in determining the viability of the neonate; the IRB is not required to approve the procedure for assessing infant viability. The responsibility for operationalizing and documenting "viability" falls to the investigator. The viability of the neonate remains a Part B regulatory issue until viability has been determined or until day 29 of life, whichever comes first.

F. Research Involving Nonviable Neonates

After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

i. Vital functions of the neonate will not be artificially maintained;

ii. The research will not terminate the heartbeat or respiration of the neonate;

iii. There will be no added risk to the neonate resulting from the research;

iv. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

v. The legally effective informed consent of both parents of the neonate is obtained. Please note that, under both Illinois law and federal regulations, minor parents have the same rights as any adult parent to consent to research involving their children. However, 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 to meet the regulatory requirements, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. There are no provisions for obtaining consent of a LAR of either or both of the parents of a nonviable neonate.

When the study interventions for a neonate would need to begin shortly after delivery, seeking parental consent/permission prior to delivery is acceptable, and in some cases could be preferable. Under some circumstances, it could be acceptable to obtain parental consent/permission during the second trimester. In some cases, it would be preferable to re-confirm parental permission shortly before the intervention is administered.

G. Research Involving, after Delivery, the Placenta, the Dead Fetus or Fetal Material

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. Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord. Furthermore, if information associated with material described above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals fall under the Federal definition of "human subject."

i. Separation of Abortion from Research

NIH guidelines require that the decision to terminate a pregnancy and the procedures of abortion should be kept independent from the retrieval and use of fetal tissue for research purposes. In addition, the timing and method of abortion should not be influenced by the potential uses of fetal tissue for transplantation or medical research. However, Illinois law prohibits fetal tissue obtained from an elective abortion to be used in research.

ii. Prohibiting Payments and Other Inducements

NIH guidelines prohibit payment and other forms of remuneration and compensation for the procurement of fetal tissue, except payment for reasonable expenses occasioned by the actual retrieval, storage, preparation, and transportation of the tissues.

iii. Informed Consent

NIH Guidelines further indicate that,

a. potential recipients of such tissues, as well as research and health care subjects, should be properly informed about the source of the tissues in question;

b. the decision and consent to abort must precede discussion of the possible use of the fetal tissue and any request for such consent that might be required for that use;

c. fetal tissue from induced abortions should not be used in medical research without the prior consent of the pregnant woman [her decision to donate fetal remains is sufficient for the use of tissue, unless the father objects (except in cases of incest or rape]; and

d. consent should be obtained in compliance with state law and with the Uniform Anatomical Gift Act.

iv. Prohibiting Directed Donations

NIH guidelines additionally require that:

a. the pregnant woman should be prohibited from designating the transplant recipient of the fetal tissue;

b. anonymity between donor and recipient should be maintained, so that the donor does not know who will receive the tissue, and the identity of the donor is concealed from the recipient and transplant team; and

c. experimental transplants performed with fetal tissue from induced abortions provided by a family member, friend, or acquaintance should be prohibited.

H. Use of Human Embryos for Stem Cell Research

In accordance with the most recent guidance on the use of human embryonic stem cells in research published by OHRP, the following guidance is offered:

i. All clinical research involving drugs, devices, and biological products regulated by FDA, including cells or test articles regulated as drugs, devices, and biological products, is also subject to FDA regulations governing investigational new drugs (INDs) or investigational new devices (IDEs) (Title 21 CFR Parts 312 or 812), regardless of the source of support. This clinical research is also subject to FDA's IRB and informed consent regulations (Title 21 CFR Parts 50 and 56).

ii. In addition, clinical research involving the transplantation of cells or test articles derived from human fetal tissue into human recipients is subject to Public Law 103-43, "Research on Transplantation of Fetal Tissue" (42 U.S.C. § 289g–2(a)).

iii. Other Federal, State or local laws may also apply to transplantation or other research involving these cells or test articles from fetal tissue that may be conducted with Federal support.

iv. Research on existing human embryonic stem cell lines may be conducted with Federal support if the cell lines meet the U.S. President's criteria.

Generally, the use of human embryonic stem cells from established cell lines does not meet the definition of human subject, as these specimens can be shared or purchased without releasing identifying information on the donor. However, in accordance with IRB policy, the investigator cannot make this determination alone. The investigator must submit an inquiry requiring an evaluation of the requirement for prior IRB review. As part of the inquiry, the investigator will be asked to describe how the stem cell lines will be obtained, identify the source of the line, and clarify whether any identifying information about the donor will be released with the specimens.

On March 9, 2009, President Barack Obama issued Executive Order 13505; entitled "Removing Barriers to Responsible Scientific Research Involving Human Stem Cells" (see http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf). The March 9, 2009 Executive Order revoked two items: the presidential statement of August 9, 2001; and Executive Order 13435 that had been issued in June 2007.

The March 9, 2009 Executive Order changed the way that the National Institutes of Health (NIH) can support and conduct human stem cell research. To implement the revised policy

embodied in the 2009 Executive Order, NIH issued Guidelines on Human Stem Cell Research (these can be found at http://stemcells.nih.gov/policy/2009guidelines.htm). The NIH Guidelines on Human Stem Cell Research require written informed consent in all cases from the individuals donating the embryos. (In contrast, OHRP's "Guidance on Research Involving Coded Private Information or Biological Specimens" states that consent is not generally required if the cells cannot be linked to specific living individuals by the investigators, either directly or indirectly through coding systems.) In addition, NIH made a policy decision to honor any restrictive language in the informed consent signed by individuals donating human embryos for research, such as statements limiting research using the cells to studies on a particular disease or aspect of development.

Investigators planning to undertake research using human embryonic stem cells should also review the National Academies of Science Guidelines for Human Embryonic Stem Cell Research (see http://dels-old.nas.edu/bls/stemcells/guidelines.shtml).

12.3 PROTECTIONS FOR PRISONERS

Prisoners are considered a vulnerable research population because of the potential constraints on their voluntary decision-making and the heightened possibility of coercion. Federal regulations identify prisoners as another "vulnerable" population, and Subpart C of 45 CFR 46 outlines special protections for such individuals when they are subjects of biomedical or behavioral research. The constitution of the Lurie Children's IRB does not meet Subpart C requirements and therefore cannot review research involving prisoners as research subjects.

However, the institution complies with 45 CFR 46 Subpart C, with one exception: Subpart C will not apply to non-federally funded social-behavioral research (not biomedical research) where the incarcerated participant was not a prisoner at the time of enrollment into the research. Whenever it is practicable, these subjects may continue to participate in the study that they enrolled in prior to becoming incarcerated. Because Illinois law prohibits medical, pharmaceutical or cosmetic experiments involving prisoners, subjects in this type of research who become prisoners will need to be withdrawn from the study in a manner which protects the safety and welfare of the subject. The plan for this process should be provided to the IRB for their review and approval when reporting the incarceration.

If a human subject involved in ongoing federally funded research becomes a prisoner during the course of the study, and the relevant research proposal was not reviewed and approved by the IRB in accordance with the requirements for research involving prisoners under subpart C of 45 CFR part 46, the investigator must promptly notify the IRB. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must be suspended immediately, except when it is in the best interests of the subject to remain in the research study while incarcerated.

Definition of Prisoner:

Federal regulations define a prisoner as any individual involuntarily confined or detained in a penal institution (45 CFR 46.303(c)). The term is intended to encompass the following:

i. Individuals sentenced to a penal institution under a criminal or civil statute,