Institutional Review Board Policies and Procedures Manual

SECTION 12: VULNERABLE SUBJECTS

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,

ii. Individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and

iii. Individuals detained pending arraignment, trial, or sentencing.

Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted or if they are being monitored by the penal system (i.e., probation, house arrest, halfway house, etc.). Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial. The regulatory definition of prisoner likewise includes people who are under house arrest but are mobile (i.e. are monitored with an ankle bracelet or other similar device).

12.4 PROTECTIONS FOR CHILDREN

Subpart D of 45 CFR 46 (DHHS regulations) and Subpart D of 21 CFR 50 (FDA regulations) outline special protections for children (including viable neonates). According to federal regulations, a "child" is a person who has not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

A. Risk Level Determinations

From a federal regulatory perspective, research is classified as involving *no risk, minimal risk, or greater than minimal risk*. According to the regulations [45 CFR 46.102(i)] "*Minimal risk* means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." It is the IRB's responsibility to determine whether or not research can be considered minimal risk. The investigator may request that the IRB consider designating the study as minimal risk, but the investigator may not make this determination on his or her own.

The risk categories set forth in the federal regulations below are used by the IRB when reviewing a study that involves children as subjects.

i. Research not involving greater than minimal risk. (45 CFR 46.404 and 21 CFR 50.51)

Taking into consideration the level of risk and prospect of direct benefit, the IRB can approve research that presents no greater than minimal risk to children.

ii. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR 46.405 and 21 CFR 50.52)

Taking into consideration the level of risk and prospect of direct benefit, the IRB can approve research that carries the potential for *greater than minimal risk* to children. Most importantly, the IRB must determine if the research holds out a prospect of direct benefit for the subjects. An IRB can itself approve research on children involving more than minimal risk if the proposed study presents such a prospect of benefit and "(a) The risk is justified by the anticipated benefits to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."

iii. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR 46.406 and 21 CFR 50.53)

Taking into consideration the level of risk and prospect of direct benefit, the IRB can approve research that involves greater than minimal risk and provides no potential direct benefit to individual subjects only if the study will "likely yield generalizable knowledge about the subject's disorder or condition." The study must also meet the following conditions:

a. "The risk represents a minor increase over minimal risk;

b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational experiences;

c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

d. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408." (45 CFR 46.406)

The requirement that the subject have a "disorder or condition" suggests great caution in conducting greater than minimal risk research with normal control subjects.

iv. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR 46.407)

This category of research requires the approval of the DHHS Secretary after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment. An IRB cannot approve such research on its own.

B. Guidelines for Research on Healthy Children

It is the responsibility of the research investigator to demonstrate the need for data collection in normal subjects and children in particular. Investigators should define the level of risk and defend the appropriateness of the age groups selected with regard to the need for the study and the level of risk. The use of normal children in research may invoke the use of 45 CFR 46.407 (Research not otherwise approval under 46.404, 46.405, or 46.406 which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children). In these cases, the research and the IRB's findings that the research may fall under 46.407 must be submitted to OHRP for consultation with a panel of experts and public review and comment. Typically this will be the investigator's responsibility. Only after OHRP's determination is made will the research be reconsidered by the IRB. The informed consent process should be appropriate to the level of risk and should also consider the developmental state of the child.

C. Wards of State

Any participation of Wards of the State in research studies regardless of the risk determination must have the prior approval of the Department of Children and Family Services (DCFS). Any

research conducted under 45 CFR 46.406 or 46.407 must also utilize a Research Subject Advocate, RSA, for each ward to be enrolled. **Please contact the IRB for guidance prior to enrolling Wards of the State on any research study regardless of the assigned risk determination. The IRB Chair is the designated Research Subject Advocate for the Institution.** If the IRB Chair is the PI for the study, the IRB Vice-Chair may be the RSA or may appoint an alternate as appropriate.

Also note that per the federal regulations, children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 46.407 only if such research is:

i. Related to their status as wards; or

ii. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

12.5 NON-ENGLISH SPEAKING SUBJECTS

A sizable percentage of patients who receive their medical care at the Institution identify a language other than English as their primary language, and these non-English speakers may be eligible for participation in IRB approved research. Noting that non-English speaking people, because of their language barrier, may be more vulnerable to coercion or undue influence when approached for participation in research, the IRB acknowledges that additional provision for the protection of these potential subjects must be taken to ensure that they understand the nature of their participation in research.

Federal regulations dictate, "the information that is given to the subject or the subject's representative shall be in language understandable to the subject or the representative." (45 CFR 46.116 and 21 CFR 50.20) To fulfill this requirement, OHRP strongly encourages providing potential subjects with a full consent document written in a language understandable to them. However, for studies that are not designed to target non-English speaking individuals, this may be an unreasonable requirement. As such, the IRB may allow for the use of a "short form" written consent document in research studies that anticipate that all of or the majority of their subjects will be fluent in English, but that non-English speakers may be encountered occasionally. The "short form" consent process permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. The "short form" must state, in the subject's language, that all of the required elements of informed consent have been presented orally to the subject or his/her legal representative in a language that he/she understands.

Regardless of the method used to document non-English speakers' consent to participate in the research, the IRB's preference is that a certified interpreter be used in the verbal consent process. The IRB prefers that a certified interpreter, rather than a friend or family member of the subject be used. In the event that the subject requests to have a friend or family member serve as interpreter, care should be taken to ensure that the interpreter's relationship with the subject does not adversely impact the subject's ability to make an independent decision regarding participation. Under no circumstances should a minor be allowed to serve as interpreter.

In accordance with the principle of justice outlined in The Belmont Report, federal regulations and ORIC policies prohibit blanket exclusion of individuals or populations from research for reasons unrelated to the purposes of the study and not otherwise medically or scientifically justified. The inconvenience or cost of accommodating non-English speakers is not considered sufficient justification for excluding such subjects from participation in a research study.

12.6 COGNITIVELY IMPAIRED SUBJECTS

Although federal regulations do not specifically prescribe the conditions under which cognitively impaired individuals may be enrolled as subjects of research, federal guidelines do address the issues surrounding inclusion of such subjects. They state, "*(ethicists) have argued that research should involve cognitively impaired subjects only where: (1) they comprise the only appropriate subject population; (2) the research question focuses on an issue unique to subjects in this population; and (3) the research involves no more than minimal risk. (Others) argue that research involving greater than minimal risk may be acceptable where the purpose of the research is therapeutic with respect to individual subjects and where the risk is commensurate with the degree of expected benefit.*" (1993 OPRR IRB Guidebook, Chapter 6) Generally, if neither of these conditions is met, potential subjects lacking the capacity to consent should not be included in the research. However, the IRB will consider each protocol separately to determine the appropriateness of including these individuals.

The IRB determines whether or not a non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written consent document, or if it may be conducted in subjects with consent of a legally acceptable representative, provided the following conditions are fulfilled:

- The objectives of the clinical trial cannot be met by means of a trial in subjects who can give consent personally.
- The foreseeable risks to the subjects are minimized.
- The clinical trial is not prohibited by law.
- The opinion of the IRB is expressly sought on the inclusion of such subjects, and the written opinion covers this aspect.

Central to the review of research involving cognitively impaired subjects is the review of the process of informed consent. The description of the process of informed consent in the IRB application must clearly state the level of capacity anticipated in the population to be recruited; describe how cognition will be assessed for each potential subject; and specify what steps will be followed in the event that it is determined that a potential subject is determined to lack the capacity to consent to his/her participation. In the event that a protocol seeks to recruit individuals who may display varying levels of cognition, the IRB application should describe how the process of consent will be modified to address any fluctuations in the subject's ability to consent. Illinois State law requires the consent of a legally authorized representative of a cognitively impaired individual before the cognitively impaired individual may be included in research.

12.7 HIV-POSITIVE SUBJECTS AND SUBJECTS WITH AIDS

A. Confidentiality

OHRP Guidance for Institutional Review Boards for AIDS Studies Federal guidelines indicates, "*perhaps the most sensitive aspect of AIDS research from the perspective of the rights and welfare of the subjects is the matter of confidentiality… Improper disclosure could have the most serious consequences for research participants, by threatening family relationships, job security, employability, or ability to obtain credit or insurance. In light of these risks, special precautions should be taken to preserve confidentiality, and potential subjects should be advised with care of the limits of that confidentiality, so they can make thoughtful, informed decisions, in light of their own circumstances, as to whether to participate.*" (OPRR Reports, Guidance for Institutional Review Boards for AIDS Studies, December 26, 1984)

The Report recommends that investigators and IRBs pay special attention to the design of HIV studies to ensure that administrative, management and technical safeguards are implemented to protect against unauthorized use and disclosure of information. Additionally, the Report indicates that, "where identifiers are not required by the design of the study, they are not to be recorded. If identifiers are recorded, they should be separated, if possible, from data and stored securely, with linkage restored only when necessary to conduct the research. No lists should be retained identifying those who elected not to participate. Subjects must be given a fair, clear explanation of how information about them will be handled."

B. Communicable Disease Reporting

In accordance with the Statutes of the State of Illinois, the Institution is responsible for the timely reporting of those diseases and conditions declared to be contagious, communicable and dangerous to public health as identified in the Illinois Department of Public Health Communicable Disease Code (e.g. HIV, Sexually Transmitted Infections, etc.). This full policy is available on the Medical Center's Administrative Policy SharePoint site.

Researchers that will test for one or more of the communicable diseases as identified by the Illinois Department of Public Health are required to follow this reporting policy. The informed consent documents are to state to potential participants when such reporting will occur; noting that this reporting will not include any identifiable information of the participant.

References:

1. Strong, C; Minimal Risk in Research Involving Pregnant Women and Fetuses; J Law Med Ethics. 2011 Fall; 39(3):529-38.