Office of Research Services

6. Vulnerable Populations

6.1 Policy

It is the responsibility of the IRB to ensure that procedures are in place in a research activity to protect the subjects taking part. This is especially true when a research activity involves a vulnerable population as research subjects. Special circumstances are sometimes necessary and special protections must be put in place to adequately protect vulnerable populations. This includes the categories of vulnerable subjects set down by the Federal regulations and those which might be vulnerable due to other considerations or the circumstances of the research activity itself. These populations include, but may not be limited to, pregnant women, human fetuses and neonates, prisoners, children, persons with physical or mental impairments, economically and/or educationally disadvantaged, persons with impaired capacity to consent, and students or employees of the institution.

6.1.1 Definitions

The following definitions apply throughout this Guidance document:

Vulnerable population: any population at risk for coercion or undue influence that may require special protections. A vulnerable population may have a limited ability to make a free and uninfluenced decision to consent to participate in research.

6.2 Specific Policies

6.2.1 Applicability

The following policies reflect Federal law and the laws of the State of Missouri. It is the responsibility of the PI when doing research with vulnerable populations in a different state to be aware of the local laws defining and regulating vulnerable populations.

6.2.2 Research Involving Pregnant Women, Human Fetuses, and Neonates

6.2.2.1 Definitions

The following definitions, as set down in 45 CFR 46.202, apply throughout this section:

Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

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

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. The Secretary of the Department of Health and Human Services may from time to time, taking into account medical advances, publish in the Federal register guidelines to assist in determining whether a neonate is viable for purposes of this Subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of the common rule and 45 CFR 46 Subpart D.

6.2.2.2 Pregnant Women or Fetuses may be Involved in Research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

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

4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained;

5. If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

6. The pregnant woman and the father, if applicable, are fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

7. For children who are pregnant, assent and permission are obtained in accord with the provisions of Subpart D of the DHHS regulations (section 6.2.4.4.3);

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.

6.2.2.3 Research Involving Neonates

Neonates of uncertain viability and nonviable neonates may be involved in research if all the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;
2. Each Individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;
3. Individuals engaged in the research will have no part in determining the viability of a neonate;
4. The additional requirements for research involving neonates of uncertain viability or non-viable neonates (see below) have been met as applicable.

6.2.2.4 Neonates of Uncertain Viability

Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this Subpart unless the following additional conditions have been met:

The IRB determines that:

1. 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**
2. 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**
3. The legally effective consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective consent of either parent's legally authorized representative is obtained, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

6.2.2.5 Nonviable Neonates

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

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;

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

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

5. The legally effective consent of both parents of the neonate is obtained in accordance with Subpart A of the regulations, except that the waiver and alteration provisions for consent do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, 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 the requirements of this paragraph.

6.2.2.6 Viable Neonates

A neonate, after delivery, which has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of this policy, research involving children (Subparts A and D of the DHHS Regulations).

6.2.2.7 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.

If information associated with material described in this section 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 are research subjects, and all pertinent sections of this policy are applicable.

6.2.3 Research Involving Prisoners

The ability of prisoners to make a free, unbiased and uncoerced decision about whether or not to participate in research is limited because of their status as incarcerated Individuals. In the history of research in the United States and abroad, prisoner populations have been exploited because of their convenience: they provided large groups of subjects located in one place largely observing the same routines and receiving roughly the same standard of care. These criteria remain largely the same today. It is therefore incumbent upon this institution and its research community to ensure that prisoners are safeguarded appropriately, to ensure that they have the ability to voluntarily determine whether they choose to participate in research.

6.2.3.1 Definitions

The following definitions, as set down in 45 CFR 46.303 apply throughout this section:

Prisoner means any Individual involuntarily confined or detained in a penal institution. The term is intended to encompass Individuals sentenced to such an institution under a criminal or civil

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

Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

6.2.3.2 Applicability

The requirements in this section apply to all research involving prisoners under the purview of the institution's IRB, regardless of the funding source. In addition to this policy, all research involving prisoners is subject to state and local laws.

6.2.3.3 Exempt Research

As set down in 45 CFR 46.104(b)(2), the permitted exemption categories for research do not apply to research involving prisoners.

6.2.3.4 Composition of the IRB

In addition to satisfying all other general requirements regarding composition, an IRB shall also meet the following specific requirements when actively conducting a review of research involving prisoners:

1. A majority of the board (exclusive of prisoner members) shall have no association with the prison(s) or facility(s) involved, apart from their membership on the board.

2. At least one member of the board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. **In the absence of choosing someone who is a prisoner or has been a prisoner, the IRB should choose a prisoner representative who has a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner.** When reviewing research that involves prisoners, the IRB must meet the above special composition requirements for all types of review of the protocol, including initial review, continuing review, review of protocol amendments, and review of reports of Unanticipated Problems or Adverse Events involving risks to subjects.

6.2.3.5 Additional Duties of the IRB

In addition to all other IRB responsibilities prescribed in this document, the board shall review research involving prisoners and approve such research only if it finds that:

1. The research under review falls into one of the following categories of research permissible under 45 CFR 46.306(a)(2):

    - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

- Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults); or

- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

3. The risks involved in the research are commensurate with risks that would be accepted by volunteers who are not prisoners;

4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

5. The information is presented in language which is understandable to the subject population;

6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

7. Where the board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of Individual prisoners' sentences, and for informing participants of this fact.

6.2.3.6 Research Conducted or Supported by DHHS

In instances where the research is conducted or supported by DHHS, research involving prisoners can only be conducted if:

1. The IRB certifies to the secretary of DHHS, via OHRP, that the IRB has reviewed and approved the research under 45 CFR 46.305; **and**

2. The secretary determines that the proposed research falls within one of the categories of permissible research listed above in section 2.2.4(1).

6.2.3.7 When Subjects Become Prisoners During Research

It is the responsibility of the PI to assess the likelihood of non-prisoner subjects becoming prisoners during the course of a research study. The PI should determine the likelihood that a subject could be reclassified as a prisoner subject in the middle of the research (e.g., in a study involving parolees with a high likelihood of re-offense) and whether that subject will remain in the study or be withdrawn. In the former case, the PI should make sure the research is initially reviewed and approved as prisoner research by the IRB if possible. If a subject in a research protocol becomes a prisoner during the time in which he or she is actively participating in the study and the protocol has not been approved for the inclusion of prisoners, then the following steps must occur:

1. The PI must immediately notify the IRB in writing of the subject's status change, and whether the subject was withdrawn or remains in the study.

2. If the PI requests that the subject remain in the study, the IRB must re-review the protocol in accordance with the policy as written in the above sections.

3. If the IRB determines that the research is not approvable as prisoner research, then the subject must be withdrawn from the study.

6.2.4 Research Involving Children

Enrolling children in research presents especially difficult considerations for IRBs. Two factors make a case for research about children: children differ markedly from adults, and therefore, these models cannot substitute as alternatives to testing with children; and lack of appropriate research with children will increase their risk of harm from exposure to practices and treatments untested in this population. In addition, new interventions could not be developed for conditions that specifically affect children. However, research in children requires that the IRB carefully consider respect for persons, beneficence, and justice.

The determination of risk (possible harms) and possible benefit to the child is at the core of the concept of beneficence when considering research in a pediatric population.

Therefore, the IRB must consider the degree of risk and discomfort involved in the research in relation to the direct benefits it offers to the child before it can determine whether or not the IRB has the authority to approve the study.

6.2.4.1 Definitions

The following definitions, as set down in 45 CFR 46.402 apply throughout this section:

Children are persons who have 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. In Missouri, a child is any person, regardless of physical or mental condition, under eighteen years of age [MO RS 210.110(4)].

Missouri law is silent with respect to the legal age of consent with respect to research. For purposes of these SOPs, any person who is under the age of 18 generally is unable to consent for him/herself. Several important exceptions exist under Missouri law that effectively treat children as adults and gives them the capacity to consent to their own medical care and to participate in research. They include the following:

- For a child to receive medical care or other, limited, social services, if:
    - The child is sixteen or seventeen years of age; and
    - The child is homeless, or a victim of domestic violence; and
    - The child is self-supporting, such that the minor is without the physical or financial support of a parent or legal guardian; and
    - The minor's parent or legal guardian has consented to the minor living Independent of the parents' or guardians' control. Consent may be expressed or implied, such that:
        - Expressed consent is any verbal or written statement made by the parents or guardian of the minor displaying approval or agreement that the minor may live Independently of the parent's or guardian's control;
        - Implied consent is any action made by the parent or guardian of the minor that Indicates the parent or guardian is unwilling or unable to adequately care for the minor. [MO RS. 431.056]
- For a child to receive medical and/or surgical care at a hospital and/or to receive physicians' services, if the child is married and/or a parent [MO RS. 431.061]. This may or may not overlap with the proposed research;
- If a child seeks treatment for pregnancy [MO RS. 431.061]
- If a child seeks treatment for venereal disease [MO RS. 431.061]; and
- If a child seeks treatment for drug abuse [MO RS. 431.061].

Because Missouri law does not specifically address consent of children with majority status to Research, the University's IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research.

Parent means a child's biological or adoptive parent.

Guardian means an Individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

6.2.4.2 Exempt Research

The exemptions at 45 CFR 46.104(d)(1) and (d)(4) through (d)(8) are applicable to research involving children. The exemption at 46.101(d)(2)(i) and (ii) regarding educational tests is also applicable for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed. However, the exemption at 46.101(d)(2)(iii) for research involving survey or interview procedures or observations of public behavior does not apply to research involving children.

6.2.4.3 Allowable Categories of Research

Research on children must be reviewed and categorized by the IRB into one of the following groups:

1. *Not greater than minimal risk*: research on children not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., minimal risk). This includes adequate provisions for soliciting the assent of the children and the permission of their parents or legal guardians as set forth below in section 6.2.4.4 (45 CFR 46.408).

2. *Greater than minimal risk:* research on children involving greater than minimal risk but presenting the prospect of direct benefit to the Individual subject. In order to approve the research, the IRB must determine if:

   2.1. The risk is justified by the anticipated benefit to the subjects;

   2.2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

   2.3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in section 6.2.4.4.

3. *Greater than minimal risk & no prospect of direct benefit:* research on children involving greater than minimal risk and no reasonable prospect of direct benefit to the Individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. The IRB must determine:

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

   3.2. 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 situations;

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

3.4. Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in section 6.2.4.4.

4. *Research not otherwise approvable:* research on children not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.

4.1. Federally funded research in this category must be approved by the DHHS secretary, in consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, or law), and requires consent of either both parents or the legal guardian. Non-Federally funded research may be approved by the IRB in the same manner. To approve the research, the secretary or IRB must determine:

- That the research in fact satisfies the conditions of the previous categories, as applicable, or the following:
  - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
  - The research will be conducted in accordance with sound ethical principles; and
  - Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in section 6.2.4.4.
- FDA-regulated research in this category must be approved by the FDA commissioner.

6.2.4.4 Parental Permission and Assent

6.2.4.4.1 Parental Permission

Since a child cannot consent for him/herself, the IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or legal guardian, as documented in the consent form.

Where parental consent is to be obtained, the IRB may find that the consent of one parent is sufficient for minimal risk research or research presenting the prospect of direct benefit to the child. Both parents must give their consent for all other research involving their child, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Parents or legal guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in the policy on consent.

For research not covered by FDA regulations, the IRB may waive the requirement for obtaining consent from a parent or legal guardian if:

1. The research meets the provisions for waiver of consent in adult research, or

2. If the IRB determines that the research protocol is designed for conditions or a subject population for which parental or legal guardian consent is not a reasonable requirement to protect the subjects (e.g., neglected or abused children) provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, state, or local laws. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Parental consent may not be waived for research covered by the FDA regulations.

Permission by parents or guardians shall be documented in accordance with and to the extent required by 46.117 of subpart A of 45 CFR part 46. Essentially, parental permission should be documented in a manner similar to that used to document informed consent. An Institutional Review Board (IRB) may find that waiver of documentation of informed consent is appropriate under the HHS regulations at 46.117.

6.2.4.4.2 Assent from Children

Because assent means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for consent by adults or for parental consent. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (e.g., what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

The IRB presumes that children ages 7 and older should be given an opportunity to provide written assent. Generally, oral assent through the use of a script should be obtained from children under 7 years of age. If a written assent form is used for older children, it should be specifically tailored to the ages of the children and their level of understanding.

At times there may be inconsistency between parent consent and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are Individual exceptions to these guidelines (such as when the use of an experimental treatment for a life-threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents' consent to it.

6.2.4.4.3 Consent from Pregnant Minors

A minor may consent to medical care or the administration of medication by a hospital licensed to provide hospital services or by a physician licensed to practice medicine for the purpose of alleviating or reducing pain, discomfort, or distress of and during labor and childbirth. [MO RS. 431.061(4)(a)]. This consent shall be valid and binding as if the minor had achieved her majority, and it shall not be subject to a later disaffirmance by reason of her minority.

If research pertains to such permitted minor consent, then the minor may consent to the involved research. If not, and the IRB has not waived the consent requirement, then assent from the minor is required, as well as parental consent.

6.2.4.4.4 Assent Form

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should include as many of the requirements for adult consent as possible, worded appropriately for the above considerations.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

6.2.4.4.4.1 Waiver of Assent

The regulations at 45 CFR 46.408(a) identify three types of circumstances where the IRB may determine that waiver of children's assent is appropriate:

- if the capability of some or all of the children is so limited that they cannot reasonably be consulted;

- if the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research.
- if the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d).

6.2.4.4.4.2 Documentation of Assent

The HHS regulations do not require documentation of assent. The Institutional Review Board (IRB) has the discretion to determine the appropriate manner, if any, of documenting child assent. Based on such considerations as the child's age, maturity, and degree of literacy, the IRB should decide what form of documentation, if any, is most appropriate. If adolescents are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent's assent.

6.2.4.4.5 Children Who are Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in research involving greater than minimal risk where there is no prospect of direct benefits to Individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, only if such research is:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed by the IRB for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian.

The advocate must be an Individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

6.2.5 Research Involving Other Potentially Vulnerable Populations

Although Federal regulations list specific vulnerable groups, other potentially vulnerable groups may include, but not be limited to, mentally impaired persons, employees of the sponsor or investigator, terminally ill patients, and the very elderly. The IRB will determine special protections for these groups on a case-by-case basis, taking into account the risks and benefits and other protections afforded by institutional policies and state and Federal law.

6.2.5.1 Persons with Impaired Decision-Making Capacity

The requirements in this section apply to all research involving persons with mental disabilities or persons with impaired decision-making capacity regardless of funding source. The majority of studies conducted at the University only allow enrolling subjects who have the capacity to consent.

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. Only incompetent persons or persons with impaired decision-making capacity (as determined by licensed health care professionals who are qualified to make such determinations consistent with the scope of their license) are suitable as research subjects. Competent persons are not suitable for the proposed research. The PI must demonstrate to the IRB that there is a compelling reason to include incompetent Individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.

2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the subject. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

3. Procedures have been devised to ensure that the subject's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision-making capacity. Health agents (appointed under medical power of attorney) and next-of-kin, or legal guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest. In addition, and as appropriate, if assent can be obtained by a subject/potential subject with diminished decision-making capacity (versus impaired), then the PI should obtain such assent. The determination as to whether an Individual retains capacity to assent must be determined by a duly qualified health care provider, consistent with the provider's scope of licensure.

4. 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. Non-therapeutic clinical trials may be conducted in incompetent subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

    - The objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;
    - The foreseeable risks to the subjects are low;
    - The negative impact on the subject's well-being is minimized and low;

- The 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;
- Unless an exception is justified, the trial should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in such trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

6.2.5.1.1 Determination of Decision-Making Capacity

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

Decisional capacity in the research context has been interpreted by the American psychiatric association as requiring:

- Ability to evidence a choice;
- Ability to understand relevant information;
- Ability to appreciate the situation and its likely consequences; and
- Ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. The PI and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate. In general, the consent assessor should be a researcher or consultant qualified to assess and monitor capacity and consent in such subjects on an ongoing basis.

For some types of research, the PI may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time. For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, consent. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the PI can justify why such assessments would be unnecessary for a particular group.

If the reason for lack of capacity is because of mental illness, then the IRB may require that a psychiatrist or licensed psychologist confirm this judgment and document it in the Individual's medical record in a signed and dated progress note.

For research protocols involving subjects who have fluctuating or limited decision-making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. A periodic re-consenting process may be considered necessary in some cases. Third party consent monitors may be used during the recruitment and consenting process or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairment to make voluntary and decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audiotaping of consent interviews, second opinions, use of independent consent observers, interpreter for hearing-impaired subjects, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision-making process.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be notified. The potential subject should be informed about the study to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written consent form or a separate assent form. Although incompetent to provide consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate. If a person objects to participating, this objection must be respected.

In the event research participants become incompetent or impaired in decision making capacity after enrollment, the PI is responsible for notifying the IRB. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision-making research participants.

6.2.5.1.2 Consent by a Third Party

The regulations generally require that the investigator obtain consent from subjects. Under appropriate conditions, investigators also may obtain consent from a third party.

This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity.

Missouri state law stipulates:

1. When an adult person, because of a medical condition, is treated by a teaching hospital for a medical school accredited by the American osteopathic association or the American medical association and such person is incapable of giving consent for an experimental treatment,

test or drug, then such treatment, test or drug may proceed upon obtaining consent of a legal guardian, attorney-in-fact, or a family member in the following order of priority:

i) Spouse unless the patient has no spouse, or is separated, or the spouse is physically or mentally incapable of giving consent, or the spouse's whereabouts is unknown, or the spouse is overseas;

ii) Adult child;

iii) Parent;

iv) Brother or sister;

v) Relative by blood or marriage.

2. Nothing in this section shall authorize such legal guardian, attorney-in-fact, or family member to consent to treatment in contravention to such incapacitated person's expressed permission regarding such treatment.

3. In a life-threatening emergency, consent of such an incapacitated person to any research program or experimental procedure shall not be required when the Institutional Review Board responsible for the review, approval, and continuing review of the research activity has approved both the research activity and a waiver of consent and has both found and documented that the requirements for an exception from consent requirements for emergency research, as provided under part 50 of title 21 or part 46 of title 45 of the code of Federal regulations, as amended, have been satisfied. [MO RS. 431.064]

6.2.5.2 Research in Mental Health Facilities

No biomedical or pharmacological research shall be conducted in any mental health facility or mental health program in which people may be civilly detained pursuant to Missouri state revised statutes, chapter 632 or in any public or private residential facilities or day programs operated, funded or licensed by the department for persons affected by intellectual disabilities, developmental disabilities, mental illness, mental disorders or alcohol or drug abuse unless such research is intended to alleviate or prevent the disabling conditions or is reasonably expected to be of direct therapeutic benefit to the participants. Without a specific court order, no involuntary patient shall consent to participate in any biomedical or pharmacological research. The application for the order shall be filed in the court having probate jurisdiction in the county in which the mental health facility is located, provided, however, that if the patient requests that the hearing be held by the court which has committed the patient, or if the court having probate jurisdiction deems it appropriate, the hearing on the application shall be transferred to the committing court. [MO RS. 630.192]

6.2.5.3 Research with Students or Employees of the Institution

Students are often a convenient subject population, based on their proximity to the investigator, and ease of access. However, when the investigator is a faculty member or other figure of authority this raises issues of possible coercion and undue influence. It is the PI’s responsibility,

with guidance from the IRB, to mitigate any perceived chances for coercion and allow students or employees to make a free and decision whether to participate in research.

6.2.5.4 Other Vulnerable Populations

The IRB will review each research protocol on its own merits and determine whether the population being studied qualifies as vulnerable, based on their circumstances and situation. If the IRB determines that the population is in fact vulnerable, the IRB may require that additional protective measures be enacted before the research is approved and may proceed.

No exhaustive list of potentially vulnerable populations exists as any given population may potentially be vulnerable based on the specifics of the planned research. The following, although not exhaustive, represents potentially vulnerable populations:

- physically and/or mentally impaired persons,
- economically and/or educationally disadvantaged,
- persons with impaired capacity to consent, and
- students or employees of the institution.

6.2.5.5 IRB Composition

If the IRB regularly reviews research involving a vulnerable category of subjects, one or more Individuals who are knowledgeable about and experienced in working with these subjects should be included as IRB members. Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population. The IRB may also utilize outside expert consultants as necessary to ensure appropriate scientific expertise.

References

The Belmont Report

45 CFR 46: Subparts B, C, D

21 CFR 56.111

OHRP IRB Guidebook

21 CFR 50 Subpart D

34 CFR 97 Subpart D

Approved by: Yusheng (Chris) Liu, PhD
Name of University Institutional Official

March 21, 2023

Signature of University Institutional Official Date