IRB Policy 15: Vulnerable Populations
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I. Summary

It is the responsibility of the ETSU IRBs to ensure the procedures are in place in a research activities to protect the subjects taking part. This is especially true when a research activity targets vulnerable individuals as subjects. The ETSU and ETSU/VA IRB determines and documents that appropriate additional safeguards are in place to protect vulnerable populations as stipulated in the federal regulations and subjects likely to be vulnerable to coercion or undue influence due to other considerations or circumstances of the research activity itself.

Some populations that might be considered vulnerable and needing additional safeguards include children, prisoners, individuals with impaired decision-making capacity, students or employees of the University, or economically or educationally disadvantaged persons. Individuals or populations that might be temporarily or permanently vulnerable include, but are not limited to, those who:

- Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged)
- Lack comprehension of the research and its risks (e.g., educationally disadvantaged, or subjects with dementia, schizophrenia, or depression)
- Have increased susceptibility to harm from the procedures of the specific study under review (e.g., individuals who would have to answer study survey questions about their sexual assault)
- Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status)

In reviewing research projects, the IRB will determine that inclusion and exclusion criteria are adequately justified and additional safeguards are implemented to minimize risks. The appropriate checklist(s) section of the relevant reviewer xform will be completed by the IRB Chair or Primary Reviewer to document the IRB determinations for each study. For full board review, the IRB minutes will document the IRB's determinations required by the regulations for research involving children, pregnant women, fetuses, neonates, or prisoners. In addition, the IRB minutes will document required determinations regarding waiver of informed consent or waiver of documentation of informed consent. The minutes will also document the protocol specific findings justifying the determinations.

When the ETSU or ETSU/VA IRB reviews research targeting vulnerable subjects, the proposal will be reviewed by one or more individuals who are knowledgeable about or experienced in working with these subjects. In addition, research with pregnant women/fetuses will be reviewed by one or more individuals who are knowledgeable about or experienced in working with these subjects.

II. Research Involving Adults with Impaired Capacity to Consent

The requirements of this section apply to all research involving persons with mental disabilities or persons with impaired capacity to consent for themselves regardless of funding source. This includes adult subjects who are incompetent to consent, cognitively impaired, or have reduced or impaired decisional capacity due to environment or situation. The ETSU IRBs recognize that enrollment of incompetent subjects may involve varying circumstances and degrees of incompetence. For example, a subject may be considered mentally/cognitively impaired (e.g. psychiatric disorder) and have the capacity to consent to or refuse to participate in research. However, a mentally/cognitively impaired subject may lack decisional capacity, in which case the subjects cannot consent for themselves for the research.

In making determinations regarding research with cognitively impaired participants, the IRB will consider the level of risk, the potential benefits, and the degree of cognitive impairment of the participant. The committee will review the proposed research, considering all applicable IRB Policies and Procedures. The IRB must ensure that additional safeguards are in place to protect the rights and welfare of this vulnerable population.

Definitions:

“Incompetence” is a legal term meaning inability to manage one’s own affairs. Often used as a synonym for incapacity.

“Cognitively Impaired” means having a psychiatric disorder (e.g. psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g. dementia, delirium) or a developmental disorder (e.g. autism) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases 98 affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

“Impaired Decisional Capacity” means having the ability to provide informed consent to or refusal of medical treatment but this ability is compromised by external factors. To give informed consent the subject must be given all relevant information pertinent to the decision and be able to recognize that a decision is needed, and process the information (i.e. discuss it, remember it, evaluate the various factors, and understand

the consequences). This process may be compromised due to external factors such as time limitations or stress.

Requirements for VA Research

For VA studies only, research involving persons with impaired decision-making capacity will only be approved when the following conditions apply:

Individuals who lack decision-making capacity may be enrolled in VA research where:

(1) The IRB determines that the proposed research entails:

(a) No greater than minimal risk to the subject; or

(b) Presents a greater probability of direct benefit to the subject than harm to the subject; or

(c) 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 that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

(2) In addition to satisfying the conditions above, the IRB determines that:

(a) The research cannot be performed solely with persons who possess decision-making capacity and the focus of the research is the disorder leading to the subjects' lack of decision-making capacity, whether or not the lack of decision-making itself is being evaluated (e.g., an individual who lacks decision-making capacity as the result of a stroke can participate in a study of cardiovascular effects of a stroke); **or**

(b) The subject of the research is not directly related to the subjects' lack of decision-making capacity but the investigator has presented a compelling argument for including such subjects (e.g., transmission of methicillin-resistant staphylococcus aureus infections in a nursing home where both individuals with and without decision-making capacity are affected).

The IRB must make a determination in writing of each of these criteria.

Requirements for non-VA studies

Non-VA research involving persons with impaired decision-making capacity will only be approved when the following conditions apply.

1. There is a compelling reason for inclusion of persons with cognitive impairment or impaired decision making capacity in the research study.
2. The PI's plan to identify those who have limited ability to consent or who are unable to consent is appropriate.
3. The PI's plan to evaluate and address changes in consent capacity during the study is appropriate.

4. The PI's plan to identify who is authorized to give legally valid consent on behalf of any individual who is determined to be incapable of giving their own consent is appropriate.
5. If the research will be conducted outside of the state of Tennessee, PI has submitted a legal opinion regarding the applicable state(s) definition of LAR and any state laws regarding research with cognitively impaired participants and the IRB has determined that the research is approvable given these state laws.
6. The PI's plan to ensure that the LAR is informed regarding his/her role and obligations is appropriate.
7. The PI's plan to obtain assent, if utilizing LAR for consent, is appropriate OR waiver of assent is granted by the IRB. (see following section)
8. The PI's plan to observe for dissent and stop study procedures for those who dissent is appropriate.

If institutionalized individuals will be involved, the IRB must consider the rationale and justification for involvement of institutionalized participants.

A. IRB Submission and Review

Investigators of proposed research involving cognitively impaired participants must submit the supplemental for cognitively impaired section of the VA xform for VA studies or the supplemental for cognitively impaired section of the non- VA xform for non-VA studies. In addition to completing the required forms documenting whether the study meets criteria 45 CFR 46.111 for approval, the IRB primary reviewer completes the reviewer section for cognitively impaired on the relevant xform for VA studies and the reviewer section for cognitively impaired on the relevant xform for non-VA studies.

B. Determination of 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. In general, the research staff must perform or obtain and document a clinical assessment of decision-making capacity for any subject suspected of lacking decision-making capacity. The IRB must review and approve the plan to ensure that it is appropriate given the population and setting of the research. ***NOTE:*** *Individuals ruled incompetent by a court of law are considered to lack decision-making capacity.*

The ETSU IRBs recognize that for some subjects, their decision-making capacity may fluctuate during the course of the research. It is the responsibility of the PI to monitor the decision-making capacity of subjects enrolled in research studies to determine if a capacity assessment is appropriate. If subjects enrolled in the research develop the capacity to provide informed consent, the IRB may require consent of the subject in accordance with 45 CFR 46.116.

C. Documenting Consent and Assent

When planning to enter subjects with impaired decision-making capacity, investigators must address in the protocol how they will determine when consent from a Legally Authorized Representative, or "LAR," will be required. When the potential subject is determined to lack decision-making capacity, investigators must obtain consent from the LAR of the subject in accordance with IRB Policy 13, unless waived.

Responsibilities of LARs

LARs are acting on behalf of the potential subjects, therefore:
(1) LARs must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision.
(2) If the potential subjects' wishes cannot be determined, the LARs must be told they are responsible for determining what is in the subjects' best interest.

Dissent or Assent

If feasible, the investigator must explain the proposed research to the prospective research subject even when the LAR gives consent. Although unable to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent. When the IRB determines that assent is required, assent shall be documented by having the subject sign and personally date the written informed consent.

Waiver of Assent

The IRB may waive the requirement for assent of the subject when:

- ✓ The capability of some or all of the subjects is so limited that they cannot reasonably be consulted;
- ✓ In determining whether subjects are capable of assent, the IRB shall take into account the maturity, psychological state and physical state of the subjects involved.
- ✓ This judgment may be made for all subjects to be involved in research under a particular protocol, or for each subject, as the IRB deems appropriate.
- ✓ 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 subject and is available only in the context of the research; or
- ✓ IRB determines that the assent may be waived according to the same criteria by which consent may be waived.

D. Required IRB Composition

When reviewing research involving individuals with questionable capacity to consent, the IRB will include at least one voting member or a non-voting consultant, independent of the research and investigators, with appropriate professional

background, knowledge, and experience in working with individuals with questionable capacity. The IRB may utilize consultants to evaluate research for any issues requested by the IRB, for example, to obtain additional information regarding the circumstances in which the participant and LAR will be recruited (e.g. the long term care facility, critical care unit, or mental health center); or to obtain additional expertise regarding applicable legal and regulatory requirements for consent to research by a LAR.

For VAMC research that involves mentally disabled persons or persons with impaired decision-making capacity, the IRB membership must include at least one member who is an expert in the area of the research.

When reviewing research funded by the National Institute on Disability and Rehabilitation Research that purposely requires inclusion of children with disabilities or individual with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of these participants.

III. Research Involving Children as Subjects

Research involving children as subjects requires compliance with the Common Rule, Subpart A as well as Subpart D, which requires additional protections for children. This policy applies to all non-exempt research regardless of funding source. FDA regulated research must also comply with regulations at 21 CFR 50, Subpart D.

VA studies may not involve children unless the research has been carefully reviewed by the IRB for its relevance to VA and has been determined to not be greater than minimal risk. The VA medical facility Director must approve participation in the proposed research that includes children.

Definitions:

“Children” are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of jurisdiction in which the research will be conducted. In Tennessee, the legal age for consent is 18 years of age.

For VA studies, biological specimens and data obtained from children is considered research involving children even if de-identified. If the biological specimens or data were previously collected, they must have been collected under applicable federal policies and ethical guidelines.

“Assent” means an individual’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. In determining whether children are capable of assenting, the investigator and the IRB must take into account the ages, maturity, and psychological state of the children involved [§.46.408(a)].

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

"Parent" means a child's biological or adoptive parent.

"Guardian" means an individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care and also includes an individual who is authorized to consent on behalf of a child to participate in research.

"Emancipated Minor" means a legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation.

"Minimal Risk" means where the probability and magnitude of harm or discomfort anticipated in the proposed 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.

A. IRB Submission and Review

For studies proposing to include children as subjects, investigators must indicate that children are a study population and complete the supplemental section of the xform for to address information related to research with children. The study team makes the initial determination regarding the appropriate categories of research involving children in which the research falls, including justification as to why the categories were selected. In addition, the study team provides an explanation regarding how adequate provisions are made for soliciting the assent of the children and the permission of each parent or guardian. The IRB considers the information in the IRB application and documents its determinations on xForms or in the meeting minutes.

B. Required IRB Composition

In addition to the meeting the IRB composition and quorum requirements detailed in IRB Policy 2, whenever the IRB reviews a protocol in which children are subjects, the IRB will ensure that appropriate pediatric expertise is available to review the specific research activities. Non-voting consultants may be invited to assist with the review if additional expertise is needed.

When reviewing research funded by the National Institute on Disability and Rehabilitation Research that purposely requires inclusion of children with disabilities or individual with mental disabilities as research participants, the IRB must include at least one person primarily concerned with the welfare of these participants.

C. Assessment of Risks, Benefits

The IRB, when reviewing research involving children as participants, considers the risks and discomforts in the proposed research and assesses their justification in light of the expected benefits. When assessing the risks and benefits, the IRB should weigh the circumstances of the children under study, the magnitude of risks that may accrue from the research, and the potential benefits to the child or to society. The assessment of the probability and magnitude of harm may be different in sick children and may vary depending on the disease the child may have. When assessing possible benefits, the IRB must also consider the variability in health statuses, taking into account the current health status and the likelihood of progression to a worsened state without the research intervention.

The IRB can approve research involving children as research subjects only when it determines the research satisfies the conditions of one or more of the categories outlined below.

1) **Research not involving greater than minimal risk (45 CFR 46.404).**
   The IRB may approve research involving children and not involving greater than minimal risk, provided that the IRB finds and documents that:
   a. No greater than minimal risk to children is presented; and
   b. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
2) **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405).**
   The IRB may approve research involving children in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is likely to contribute to the participant's well-being, only if the IRB finds that:
   a. The risk is justified by the anticipated benefit to the participant;
   b. The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches; and
   c. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.
3) **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).**
   The IRB may approve research involving children in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or by a monitoring procedure that is not likely to contribute to the participant's well-being, only if the IRB finds that:
   a. The risk represents a minor increase over minimal risk;

b. The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
c. The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition that is of vital importance for the understanding or amelioration of disorder, or condition; and
d. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

4) **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).**
   a. The IRB may approve research which does not meet the requirements of the categories above only if the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and
   b. If federally funded, the Secretary of DHHS (FDA Commissioner for FDA-regulated research), after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:
      i. That the research in fact satisfies the conditions of 45 CFR §46.404, §46.405, or §46.406 {FDA: 21 CFR §50.51, §50.52, or §50.53}, as applicable, or
      ii. That the following conditions are met:
         1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
         2. The research will be conducted in accordance with sound ethical principles.
         3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 45 CFR §46.408 {FDA: 21 CFR §50.55}.

In all cases, the IRB must determine that adequate provisions have been made for soliciting the assent of children and the permission of the parents or guardians.

D. <u>Parental Permission and Assent</u>

Regulations require that the IRB determine that adequate provisions are made for obtaining and documenting the assent of the children, when in the judgment of the IRB, the children are capable of providing assent. In determining whether children are capable of assent, the IRB shall take into account the age, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in the research under a particular protocol, or for each child, as the IRB deems appropriate. When the IRB determines that assent is required, it will also determine whether and how assent must be documented. The child should be given an

explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity level, and condition.

If the IRB determines either of the following to be true, then the assent of the children is not a necessary condition for proceeding for the research:

a. The capability of some or all of the children is so limited that they cannot reasonably be consulted, or
b. 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 child and is available only in the context of the research.

Waiver of Assent

Even where the IRB determines that the participants are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

1) The research involves no more than minimal risk to the participants;
2) The waiver will not adversely affect the rights and welfare of the participants;
3) The research could not practicably be carried out without the waiver; and
4) Whenever appropriate, the participants will be provided with additional pertinent information after participation.

In addition, since children cannot consent for themselves, the IRB must find that adequate provisions are made for soliciting the permission of each child's parents or guardian. Only parents or legal guardians may grant permission for their child's participation in research. Assent is sought from the child only after parental permission is granted. Grandparents and other relatives may not grant permission unless they have been granted formal custody of the child by a court. In such cases, the PI must obtain a copy of the court order as evidence of that person's authority.

Parents and legal guardians must be provided with the basic elements of consent and any additional elements of consent the IRB deems necessary, unless waived, as described in IRB Policy 13. Permission by parents or guardians will be documented appropriately.

When parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405 (categories 1 and 2 above). For research covered by 45 CFR 46.406 and 45 CFR 46. 407 (categories 3 and 4 above) and permission is to be obtained from parents, both parents must give their permission, 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.

Waiver of Parental Permission

In addition to the waiver criteria described in IRB Policy 13, the IRB may waive the requirement for obtaining parental or guardian permission if the IRB determines that

research study is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), provided all of the following are true:

1) The research is not subject to FDA regulations,
2) The waiver is not inconsistent with federal, state, or local law, and
3) An appropriate mechanism is in place to protect the children who will participate in the research. The choice of an appropriate substitute mechanism (for example, appointing a child advocate) 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.

E. Wards of the State

Children who are wards of the state or other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 45 CFR.407 (category 3 or 4 above) only if such research is either:

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.

In research approved under 45 CFR 46.406 or 45 CFR.407 (category 3 or 4 above), the IRB must require appointment of an advocate for each child who is a ward. This advocate serves in addition to any other individual acting on behalf of the child as a guardian or *in loco parentis.* One individual may serve as advocate for more than one child. The advocate shall 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. The IRB documents determinations regarding children as wards on xForms or in the minutes.

F. Children who Turn 18 While on Study

When a child who is enrolled in research with parental or guardian permission subsequently reaches the age of consent, the subject's participation is no longer covered by this policy. Unless the IRB waives the requirements to obtain consent, the investigator must obtain informed consent from the now adult subject for continued participation in the ongoing research.

G. Pregnant Minors and Minor Parents

In Tennessee, pregnant minors cannot, by virtue of their pregnant status alone, consent on their own behalf to participate in research. Although pregnant minors cannot consent for their own participation in research, once the child is born, the

mother, even if she is still a minor, is the appropriate person to consent for her child to participate in research. Unless parental permission is waived, any minor parent can give permission for their child to participate in research, but the parent/guardian of the minor parent or pregnant minor must give permission for the minor to participate in research.

For VA studies, research involving clinical interventions with the potential of greater than minimal risk cannot be conducted by VA for children who are pregnant

IV. Research Involving Pregnant Women, Fetuses and Neonates

Research involving women who are or may become pregnant requires special consideration from the IRB to ensure ongoing safety of subjects during pregnancy, avoid unnecessary risk to the fetus, and ensure informed consent is obtained from the appropriate persons. It is the policy of the IRB to provide additional protections for pregnant women, fetuses and neonates involved in research. When research is funded by DHHS, or otherwise subject to DHHS regulations, the IRB applies the additional protections specified in 45 CFR 46 Subpart B. The IRB does not allow pregnant women, fetuses or neonates to be involved in research without specific approval of their involvement in the research.

This policy applies to the conduct of non-exempt human subjects research involving pregnant women, fetuses, and/or neonates. This policy section does not apply to the conduct of research with viable neonates. A neonate, after delivery, that has been determined to be viable (i.e., likely to survive to the point of sustaining life independently, given the benefit of available medical therapy) falls under the policy section on children in research above.

Definitions:

“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 within the first four weeks after delivery.
“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.

A. IRB Submission and Review

For studies proposing to target pregnant women, fetuses, nonviable neonates, or neonates of uncertain viability as subjects or using fetal tissue or the placenta, investigators must indicate that pregnant women/fetal tissue/placenta and/or neonates are a study population and complete the supplemental section(s) of the xform to address information related to research with these populations. The study team makes the initial determination regarding the appropriate categories of research involving pregnant women and neonates in which the research falls, including justification as to why the categories were selected. In addition, the study team provides an explanation regarding how adequate provisions are made for soliciting legally effective informed consent as appropriate for the research being proposed. The IRB considers the information in the IRB application and documents its determinations on xForms or in the meeting minutes.

B. Research involving pregnant women or fetuses

The IRB may approve research involving pregnant women or fetuses only if the IRB finds and documents that all of the following conditions are met:

a. 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;

b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; 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;

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

d. 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 in accord with the informed consent provisions of subpart A of 45 CFR 46 (and for VA, Directive 1200.05).

e. 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 in accord with the informed consent provisions of subpart A of 45 CFR 46 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.

f. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

g. No inducement, monetary or otherwise, will be offered to terminate a pregnancy.

h. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

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

For VA studies, a woman is 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.

For VA studies:
a. Research that involves provision of in vitro fertilization services can be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. This includes prospective and retrospective research involving provision of or the enhancement of FDA-approved methods of in vitro fertilization for studies involving consenting subjects, both male and female, undergoing or who have undergone in vitro fertilization for the treatment of certain forms of human infertility. In vitro fertilization is any fertilization of human ova that occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

b. Prospective and retrospective studies that enroll or include pregnant subjects who conceived through in vitro fertilization or other artificial reproductive technologies are permitted.

c. Research that uses human fetal tissue or that focuses on either a fetus, or human fetal tissue, in-utero or ex-utero cannot be conducted by VA investigators while on official VA

duty, at VA facilities, or at VA-approved off-site facilities. Use of stem cells shall be governed by the policy set by NIH for recipients of NIH research funding (https://stemcells.nih.gov/policy/2009-guidelines.htm).

d. Research involving the creation of a human embryo or embryos solely for research purposes or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498B of the Public Health Service Act (42 U.S.C. 289g(b)) cannot be conducted by VA Investigators, at VA facilities, or at VA approved off-site facilities.

e. Women who are known to be pregnant and their fetuses may be involved in research if all the requirements above are met and the VA medical facility Director certifies that the VA medical facility has sufficient expertise in women's or reproductive health to conduct the proposed research if the research includes interventional studies or invasive monitoring of pregnant women as subjects, (see guidance at https://www.research.va.gov/resources/policies/default.cfm) including informed consent requirements and the ethical and scientific criteria outlined above.

C. Research Involving Neonates

Neonatal research is dependent on the viability status of the neonate as described in this policy. Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

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

Neonates of uncertain viability

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

a. The IRB determines that:
    a. 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
    b. 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
b. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or

temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable neonates

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

a. Vital functions of the neonate will not be artificially maintained;
b. The research will not terminate the heartbeat or respiration of the neonate;
c. There will be no added risk to the neonate resulting from the research;
d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
e. The legally effective informed consent of both parents of the neonate is obtained in accordance with IRB Policy 13, except that the waiver and alteration provisions do not apply.
    a. 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
        i. The consent of the father need not be obtained if the pregnancy resulted from rape or incest.
        ii. The IRB cannot approve the consent of a LAR for a nonviable neonate.

Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Pregnant Women, Fetuses, or Neonates

The Secretary of DHHS will conduct or fund research that the IRB does not believe meets the requirements of 45 CFR 46.204 or 45 CFR 46.205 only if:

a. The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
b. The Secretary, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
    a. That the research, in fact, satisfies the conditions of §46.204, as applicable; or
    b. The following:
        i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
        ii. The research will be conducted in accord with sound ethical principles; and

iii. Informed consent will be obtained in accord with the informed consent provisions of 45 CFR 46 Subpart A and other applicable subparts of 45 CFR 46.

D. 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 (45 CFR 46.206). If information associated with such material 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 for federally funded research, all pertinent subparts of the regulations are applicable.

Tennessee Code Annotated section 39-15-208 makes it unlawful for any person or entity to engage in medical experiments, research, or taking of photographs upon an aborted fetus without the prior knowledge and consent of the mother. Additionally, no person or entity may offer or accept money or anything of value for an aborted fetus. Violations of these provisions are punishable as a Class E felony.

VA investigators cannot conduct interventions in research that include neonates while on official VA duty, at VA facilities, or at VA-approved off-site facilities. VA investigators may conduct research involving noninvasive monitoring of neonates if the research is determined by the IRB to be minimal risk. Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted.

The reviewing IRB must have the appropriate expertise to evaluate any VA research involving neonates and must comply with the requirements of 45 CFR 46.205. The VA medical facility Director must certify that the medical facility has sufficient expertise in neonatal health to conduct the proposed research.

E. Research involving Human Fetal Tissue

The Secretary of DHHS may conduct or support research using human fetal tissue (HFT) for therapeutic purposes in accordance with the following (42 USC 289g-1):

Human fetal tissue may be used only if the woman providing the tissue makes a statement, made in writing and signed by the woman, declaring that:

a. The woman donates the fetal tissue for use in research.
b. The donation is made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue.
c. The woman has not been informed of the identity of any such individuals.

Human fetal tissue may be used only if the attending physician with respect to obtaining the tissue from the woman involved makes a statement, made in writing and signed by the physician, declaring that:

I. The tissue has been donated by the woman as described above; and
II. In the case of tissue obtained pursuant to an induced abortion:
    a. The consent of the woman for the abortion was obtained prior to requesting or obtaining consent for a donation of the tissue for use in such research.
    b. No alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue.
    c. The abortion was performed in accordance with applicable state law; and
III. Full disclosure has been provided to the woman with regard to:
    a. Such physician's interest, if any, in the research to be conducted with the tissue.
    b. Any known medical risks to the woman or risks to her privacy that might be associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care.

Human fetal tissue may be used only if the individual with the principal responsibility for conducting the research involved makes a statement, made in writing and signed by the individual, declaring that the individual:

a. Is aware that the tissue is human fetal tissue, the tissue may have been donated pursuant to a spontaneous or induced abortion or pursuant to a stillbirth and the tissue was donated for research purposes.
b. Has provided such information to other individuals with responsibilities regarding the research;
c. Will require, prior to obtaining the consent of an individual to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of such information by such recipient; and
d. Has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purposes of the research.

V. Research Involving Prisoners

The ability of prisoners to make a free, voluntarily, 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 are housed in a single location, constitute a large and relatively stable population, and live a routine life. It is therefore particularly important that the institution and the research community take appropriate measures to ensure that prisoners are safeguarded appropriately when they are included as participants in research.

The federal regulations at 45 CFR 46 Subpart C provide additional protections to biomedical and behavioral research involving prisoners as participants. When research is funded by DHHS, or otherwise subject to DHHS regulations, the IRB applies the additional protections specified in 45 CFR 46 Subpart C. These safeguards apply to

research where any participant is or becomes a prisoner unless the research qualifies for exemption (and is not subject to Subpart C).

Definitions:

"Prisoner" is defined by DHHS regulations at 45 CFR 46.303 as "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 statue, individuals detained in other facilities by virtue of statues 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" for prisoner at 45 CFR 46.303(d) differs from the definition of minimal risk for other research. For human subjects research involving prisoners, the definition of 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."

A. IRB Submission and Review

Investigators of proposed research involving prisoners as participants must submit the supplemental prisoners section of the VA xform for VA studies or the supplemental prisoners section of the non-VA xform for non-VA studies. The IRB Chair completes the Chair Review xform for each new submission and selects the appropriate review level based on the risks of the research and assigns appropriate expedited or full board reviewers. If the research involves prisoners, the IRB Chair will assign a prisoner advocate reviewer as one of the reviewers, focusing on appropriate additional protections and compliance with Subpart C. In addition to completing the required forms documenting whether the study meets criteria 45 CFR 46.111 for approval, the IRB prisoner advocate reviewer completes the reviewer section for prisoner criteria on the xform for VA studies and non-VA studies. For research reviewed by the convened IRB, the assigned prisoner advocate reviewer must present their review at the meeting with the determinations recorded in the meeting minutes. Research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer.

B. Required IRB Composition

In addition to meeting the IRB composition and quorum requirements detailed in IRB Policy 2, whenever the convened IRB reviews a protocol in which a prisoner is a subject:

- A majority of the IRB (exclusive of prisoner members or prisoner advocates) must have no association with the prison(s) involved, apart from their membership on the IRB;

- At least one voting IRB member present at the meeting must be a prisoner, or a prisoner advocate/representative with appropriate background and experience to serve in that capacity.

These composition requirements must be met for all types of review of the protocol, including initial review, continuing review, review of protocol modifications, and review or unanticipated problems involving risks to participants.

C. Additional IRB Duties

In addition to all other pertinent requirements, the IRB may approve research involving prisoners only if the IRB finds and documents that all of the following conditions are met:

1. 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;
2. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
3. 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 PI provides to the IRB justification in writing for following some other procedures, control subject must be selected randomly form the group of available prisoners who meet the characteristics needed for that particular research project;
4. The information is presented in language which is understandable to the subject population;
5. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decision regarding parole; and each prisoner is clearly informed in advance that participation in the research will have no effect of his or her parole; and
6. Where the IRB 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's sentences, and for informing participants of this fact.

D. Permitted Research Involving Prisoners

The research under review represents one of the following categories of permissible research as described in 45 CFR 46 Subpart D:

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

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

c. 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

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

Waiver for Epidemiology Research Involving Prisoners

45 CFR §46 Waiver of the Applicability of Certain Provisions of Department of Health and Human Services Regulations for Protection of Human Research Subjects for Department of Health and Human Services Conducted or Supported Epidemiologic Research Involving Prisoners as Subjects (Federal Register, Vol. 68, No. 119, pp. 36929-36931, Friday, June 20, 2003)

Research that involves epidemiologic studies that meet the following criteria may qualify for a waiver of applicability from the other criteria defined in Section D above,

1. The sole purposes of the research are:
    a. To describe the prevalence or incidence of a disease by identifying all cases or;
    b. To study potential risk factor associations for a disease; and
2. Where, for federally funded studies, the institution responsible for the conduct of the research certifies to the Office for Human Research Protections (acting on behalf of the Secretary of DHHS) that the IRB approved the research and fulfilled its duties under 45 CFR §46.305(a)(2)–(7) and determined and documented that:
    a. The research presents no more than minimal risk and no more than inconvenience to the prisoner-participants, and
    b. Prisoners are not a particular focus of the research.

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the subjects. This research may be eligible for expedited review.

E. 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 Institution engaged in the research certifies to the Secretary of DHHS (through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305.
2. The Secretary (through OHRP) determines that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2), or qualifies for the epidemiologic waiver.

In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research.

To fulfill these requirements, after the IRB has reviewed and approved prisoner research supported by DHHS, the IRB Director will prepare and send to OHRP a certification letter stating:

- The IRB has been constituted according to the regulations;
- The IRB considered and made the required 7 findings set forth in 45 CFR 46.305; and
- The category of approval under 45 CFR 46.306 that permits this research to go forward with prisoners as human subjects.

The certification letter will specifically identify the research protocol and any relevant DHHS grant application or protocol. A copy of the research proposal, including the IRB-approved protocol, any relevant DHHS grant application or proposal, any IRB application forms, and any other information requested by the IRB during initial IRB review, will be sent with the letter.

OHRP will determine which permissible category, if any, under which the proposed research qualifies. OHRP is responsible for consulting with experts and/or publishing in the Federal Register as appropriate with respect to paragraphs (iii) and (iv) of 45 CFR 46.306(a)(2).

Enrollment of prisoners into a DHHS conducted or supported research study may not begin until OHRP issues its approval in writing to the institution of behalf of the Secretary. This requirement is detailed in the IRB determination letter to the investigator. A subsequent letter informing the PI that the IRB has received concurrence from OHRP will be sent by the IRB and included in the study file.

F. Participant becoming prisoner during research:

If a research participant becomes a prisoner while enrolled in a research study that was not previously approved in accordance with this policy, the Principal Investigator is responsible for notifying the IRB immediately. If the research is supported by DHHS and the proposal was not reviewed and approved by the IRB in accordance with the DHHS regulations at 45 CFR 46, Subpart C, the PI must stop all research interactions with the participant, including obtaining identifiable private information, until the requirements of Subpart C have been satisfied by the IRB. OHRP allows one exception as follows: In special circumstances in which the principal investigator asserts that it is in the best interest of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied. It is the responsibility of the investigator to immediately submit the report and include pertinent details to support the exception for consideration by the IRB Chair. The ETSU IRBs will promptly re-review the proposal in accordance with this policy if the PI wishes for the prisoner to continue to participate in the research.

G. IRB Records

The IRB will prepare and maintain adequate documentation of IRB activities regarding research involving prisoners. That documentation will include, but is not limited to, the curriculum vitae of the prisoner or prisoner representative serving on the IRB, a record of the determination of the IRB regarding the seven additional findings required under HHS regulations at 45 CFR 46.305(a) and copies of all correspondence with OHRP.

H. Additional Requirements

In addition to IRB approval, investigators must obtain approval of the Tennessee Department of Corrections (TDOC). TDOC policy number 114.02 outlines the procedures for acquiring research approval within the department. The research process within the TDOC is consistent with American Correctional Association (ACA) standards.

Because of this law, the IRB must ensure that all appropriate approvals are obtained.

Under 28 CFR 512, the Federal Bureau of Prisons places special restriction on research that takes place within the Bureau of Prisons. Additional requirements for prospective researchers to obtain approval to conduct research within the Federal Bureau are outlined.

References:

OHRP Guidance on the Involvement of Prisoners in Research
45 CFR 46.402(d)-(e)
OHRP Guidebook: Chapter VI Special Classes of Subjects
21 CFR §50.3(o)
TDOC Policy number 114.02
28 CFR 512
TN Code Annotated 39-15-208
VHA Directive 1200.05