

IRB Policy 15: Vulnerable Populations

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I. Summary

The ETSU and ETSU/VA IRB will consider certain groups of human subjects to be particularly vulnerable to coercion or undue influence in a research setting, to include children (also indirectly an infant, if mother nursing the infant is a subject of research), prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons. In reviewing research projects, the IRB will scrutinize those involving these vulnerable groups, to ascertain that their use is adequately justified, and additional safeguards are implemented to minimize risks unique to each group. Studies involving pregnant women/fetuses will be reviewed as indicated in this policy.

The appropriate checklist(s) section of the relevant reviewer xform (xForm sections 130-133 for children, Form 134 for pregnant women and fetuses, Form 135 for neonates, Form 136 for Prisoners, Form 137 for Waiver or Alteration of Requirement to Obtain Informed Consent, Form 138 for Waiver of Requirement for Written Documentation of Informed Consent) will be completed by the IRB Chair or Primary Reviewer. 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.

Any proposal engaging subjects of vulnerable categories, such as children, prisoners, individuals with impaired decision making capacity will additionally be reviewed by one or more individuals who are knowledgeable about and 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 and experienced in working with these subjects.

Where relevant, the IRB must document why it considers an individual or population to be vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of participants who are likely to be vulnerable. 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, 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).

A. Research involving the Cognitively Impaired

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).

Determination of Capacity. When planning to enter subjects with impaired decision-making capacity, investigators must address in the protocol how they will determine when surrogate consent (i.e., a LAR) will be required. 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.*

Surrogate consent. When the potential subject is determined to lack decision-making capacity, investigators must obtain consent from the LAR of the subject (i.e., surrogate consent). **NOTE:** *Investigators and IRBs have a responsibility to consult with the Office of General Counsel (OGC) regarding state or local requirements for surrogate consent for research that may supersede VA requirements.*

Authorized Person. The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority in accordance with VA regulations at 38 CFR 17.32(e), (g)(3). **NOTE:** *Consent for research is required in addition to the consent that is obtained for the patient's non-research related treatments and procedures.*

- (1) Health care agent (i.e., an individual named by the subject in a Durable Power of Attorney for Health Care);
- (2) Legal guardian or special guardian;
- (3) Next of kin: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or
- (4) Close friend.

NOTE: *The persons authorized to consent on behalf of persons who lack decision-making capacity for participation in the research may not necessarily be the same as the persons authorized to provide permission for the use and disclosure of information on a HIPAA authorization on behalf of persons who lack decision-making capacity (see VHA Handbook 1605.1).*

Dissent or Assent. If feasible, the investigator must explain the proposed research to the prospective research subject even when the surrogate 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.

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.

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.

The IRB must make a determination in writing of each of these criteria. Investigators must submit the supplemental for cognitively impaired section of the VA xform. The IRB documents these determinations on the reviewer section for cognitively impaired on the relevant xform.

For non-VA studies:

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 an LAR.

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.

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.

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 45CFR 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.

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.

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. When the IRB determines that assent is required, assent shall be documented by having the subject sign and personally date the written informed consent.

The IRB may waive the consent requirements under the circumstances described in IRB Policy 13 (see Section IV and Section VI).

B. Children

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.

Investigators must complete the Supplemental xform Section for children in the research proposal involves minors. The IRB's determinations are documented on xForms Sections 130, 132, and 133.

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
- “Assent” means a child’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)].
- “Permission” means the agreement of parent(s) or guardian to the participation of their child or ward in research.
- “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.
- “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. NOTE: In the state of Tennessee, the Age of Majority is 18 years of age.
- “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.

Assessment of Risks, Benefits

The IRB, when reviewing research involving children as participants, considers the risks, benefits, 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 the risk 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.

Federal regulations require the IRB to classify research involving children into one of four categories and to document discussion of the risks and benefits of the research study. Those four categories of research are as follows:

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. **If an IRB does not believe that research within the scope described in §§50.1 and 56.101 of this chapter and involving children as participants meets the requirements of §50.51, §50.52, or §50.53, the research may proceed only if:** [45 CFR §46.407] [21 CFR §50.54]
- a. 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.
 - b. The agency head, 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:
 - 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
 - That the following conditions are met:
 - 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.
 - 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.

Consent and Assent

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.

Waiver of Assent:

The IRB may waive the requirement for assent of some or all of the children when:

- 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

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:

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

In addition, the IRB shall require the permission of each child's parents or guardian.

Only the parents may grant permission for their child's participation in research. Assent is sought from the child only after permission has been obtained from the parent(s). 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.

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—Research not involving greater than minimal risk and research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects). For research covered by 45 CFR 46.406 and 45 CFR 46.407, (greater than minimal risk and no direct benefit or otherwise unapprovable) and permission is to be obtained from parents, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not

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reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Permission by parents or guardians will be documented appropriately.

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 (number three above) or 45 CFR.407 (number four above) only if such research is either 1) related to their status as wards or 2) be 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 (number three above) or 45 CFR.407 (number four 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 Form 131.

Research Involving Pregnant Women, Fetuses and Neonates

It is the policy of the IRB to provide additional protections for pregnant women, fetuses and non-viable neonates involved in research. The IRB does not allow pregnant women, fetuses or non-viable neonates to be involved in research without specific approval of their involvement in the research (e.g., consultation with professionals in the field).

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.

1. 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 (DHHS) 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. For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of 45 CFR 46. 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;
- h. No inducement, monetary or otherwise, will be offered to terminate a pregnancy.

- i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- j. Individuals engaged in the research will have no part in determining the viability of a neonate.

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 in which the focus is either a fetus, either in-utero or ex-utero can be conducted by VA investigators while on official VA duty, at VA facilities, or at off-site facilities. Use of human fetal tissue (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-143.html> and <https://grants.nih.gov/grants/guide/notice-files/not-od-16-033.html>) and human stem cells (<https://stemcells.nih.gov/policy/2009-guidelines.htm>) shall be governed by the policy set by NIH for recipients of NIH research funding.

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.

Neonates

Neonate means a newborn within the first 4 weeks of birth.

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.

2. 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.
- c. 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 of paragraph (b) or (c) of 45 CFR 46.205 have been met as applicable.

3. 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:
 - (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
 - (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

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 legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

4. Nonviable neonates:

Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart 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 accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), 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 (c)(5).

5. Viable neonates. If a neonate is judged viable (i.e., likely to survive to the point of sustaining life independently, given the benefit of available medical therapy), it is then called an infant and should be treated as a child for purposes of research participation. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of 45 CFR 46.

6. Research involving, after delivery, the placenta, the dead fetus or fetal material.

a. 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. Tennessee Code Annotated section 39-15-208 makes it unlawful for any person or entity to engage in the following activities without the prior knowledge and consent of the mother:

- medical experiments,
- research, or
- taking of photographs upon an aborted fetus.

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.

b. If information associated with material described in paragraph A of 45 CFR 46.206 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 subparts of the regulations are applicable.

7. §46.207: 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 the Department of Health and Human Services (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 (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

i. That the research, in fact, satisfies the conditions of §46.204, as applicable; or

ii. The following:

1. 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
2. The research will be conducted in accord with sound ethical principles; and
3. 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.

8. 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: [42 USC §498A(b)(1)]

- 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: [42 USC §498A(b)(2)]

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.

The tissue has been donated by the woman in accordance with 42 USC §498A(b)(1).

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: [42 USC §498A(c)]

- 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.

D. Research Involving Prisoners

The provisions of 45 CFR 46 Subpart C provide additional protections to biomedical and behavioral research involving prisoners as participants. These safeguards apply to research where any participant is or becomes a prisoner.

A **prisoner** is defined by HHS 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 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.”

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.

A. Required IRB Composition

Whenever the 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.

B. 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. The research under review represents one of the following categories of permissible research (45 CFR 46.306):

- 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); provided that 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;** 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. 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.**

- e. Research that involves epidemiologic studies that meet the following criteria: [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)] where
 1. The sole purposes of the research are one of the following:
 - To describe the prevalence or incidence of a disease by identifying all cases or;
 - To study potential risk factor associations for a disease.
 2. The institution responsible for the conduct of the research certifies to the Office for Human Research Protections, DHHS, acting on behalf of the Secretary that the IRB approved the research and fulfilled its duties under 45 CFR §46.305(a)(2)–(7) and determined and documented that: (Note: Certification to OHRP is required only for research conducted or sponsored by DHHS. IRBs still have to make and document the required findings.)
 - ❑ The research presents no more than minimal risk and no more than inconvenience to the prisoner-participants.
 - ❑ Prisoners are not a particular focus of the research.

* Note that the definition of minimal risk for prisoner at 45 CFR 46.303(d) differs from the definition of minimal risk for other research: For prisoner: 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.”

** Refer to section C, Research Conducted or Supported by DHHS

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 non-prisoner volunteers;

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 PI provides to the IRB justification in writing for following some other procedures, control

subject 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 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

7. 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.

C. Research conducted or supported by DHHS:

For research conducted or supported by HHS to involve prisoners, the following two actions must occur:

- i. The Institution engaged in the research must certify to the Secretary (through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305.
- ii. The Secretary (through OHRP) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2).

To fulfill these requirements, the IRB Staff will prepare and send to OHRP a certification letter stating:

- a. The IRB (including name and address) has been constituted according to the regulations;
- b. The IRB considered and made the required 7 findings set forth in 45 CFR 46.305;
- c. The category of approval under 45 CFR 46.306 that permits this research to go forward with prisoners as human subjects;
- d. Whether OHRP needs to consult with appropriate experts and publish a Federal Register Notice.

The certification letter will specifically identify the research protocol and any relevant HHS grant application or protocol. A copy of the research proposal, including the IRB-approved protocol, any relevant HHS 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.

D. Participant becoming prisoner during research:

If a research participant becomes a prisoner after enrollment in a research study, the Principal Investigator is responsible for notifying the IRB immediately. If the research proposal was not reviewed and approved by the IRB in accordance with the HHS 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.”

E. 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.

F. Additional Requirements

In addition to IRB approval, investigators must obtain approval of the TDOC. Tennessee Department of Corrections (TDOC) policy number 114.02 outlines the procedures for acquiring research approval within the department. These “Submittal instructions for research applicants” outline the guidelines as established by policy

[114.02 (VI)(C)(1) for proposing and conducting research within TDOC facilities. The research process within the TDOC is consistent with American Correctional Association (ACA) standards referenced in *Standards for Adults Correctional Institutions, third edition*. Specific ACA standards pertaining to research activities within the Department of Correction include 3-4105, 3-4106, 3-4107, 3-4108, 3-4109, 3-4110 and 3-4373.

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(e)
OHRP Guidebook: Chapter VI Special Classes of Subjects
45 CFR § 46.402(d)
21 CFR §50.3(o)
TDOC Policy number 114.02
28 CFR 512
TN Code Annotated 39-15-208
VA Directive 1200.05