

# Section 4:

# Vulnerable

# Populations

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- 4.1 Additional Protections for Vulnerable Populations
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- 4.3 Research Involving Prisoners
- 4.4 Research Involving Children
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- 4.7 Research Involving Employees of the Organization and Students as Subjects

# 4.1 Additional Protections for Vulnerable Populations

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Last Revised: 1/26/2018

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for additional protections for vulnerable populations.

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## 2.0 Policy

- **2.1.** It is the policy of the Organization that vulnerable populations will be afforded additional protections, in accordance with the ethical principles described in the Belmont Report, and the requirements of 45 CFR 46.111(b) and 21 CFR 56.111(b).
  - **2.2.** It is the policy of the Organization that the requirements for special protections specified under HHS regulations at 45 CFR 46 Subpart B (pregnant women, human fetuses and neonates of uncertain viability or non-viable), Subpart C (prisoners), and Subpart D (children) will be applied for research funded by any of the Common Rule agencies or departments.
  - **2.3.** It is the policy of the Organization that equivalent protections will be provided for the vulnerable populations described above who are participating in research not funded by any of the Common Rule agencies or departments. Equivalent protections will be based upon the ethical principles in the Belmont Report, and the requirements in 45 CFR 46, Subpart B, C, and D will be applied to the greatest extent possible in consideration of the nature of the research.
  - **2.4.** It is the policy of the Organization that the additional safeguards for children in clinical investigations under FDA regulations at 21 CFR 50 Subpart D will be applied for research regulated by the FDA.
  - **2.5.** It is the policy of the Organization that additional protections will be provided for other vulnerable populations including, but not limited to, decisionally-impaired persons, terminally ill, or economically or educationally disadvantaged persons. In these situations, the IRB, in consultation with the PI, will determine the appropriate methods to protect the rights and welfare of the individuals in consideration of the principles of the Belmont Report, the nature of the research, and other factors determining vulnerability.
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## 3.0 Definition

- **3.1. Vulnerable Persons** are defined as individuals or groups of individuals “with diminished autonomy” (National Commission, 1979) or as individuals or groups of individuals who “have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity ... or situational circumstances ..., or because they are especially at risk for exploitation” (National Bioethics Advisory Committee, 2001). Within any group of vulnerable subjects, individuals may have different levels of vulnerability based on the level of capacity, circumstance, or condition. In addition, “vulnerability is sensitive to context, and individuals may be vulnerable in one situation but not in another” (National Bioethics Advisory Committee, 2001).
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## 4.0 Categories of Vulnerability

- **4.1.** Broadly, vulnerabilities in the context of research may be considered to fall into one or more of the following types:
    - **4.1.1.** Cognitive or Communicative: diminished capacity to understand or communicate.
    - **4.1.2.** Institutional: subject to the formal authority of others.
    - **4.1.3.** Deferential: informal subordination to others (gender, race or class inequalities; inequalities of power and knowledge).
    - **4.1.4.** Medical: serious health conditions.
    - **4.1.5.** Economic and/or Social - disadvantaged in the distribution of social goods and services, or belonging to an undervalued group.
  - **4.2.** Vulnerable person may also be considered as belonging to certain groups or populations. Though useful, categorization in this manner needs to consider context and situation. Groups include, but are not limited to:
    - **4.2.1.** Pregnant women (Subpart B) (see [HRPP policy 4.2](#)).
    - **4.2.2.** Fetuses and neonates (Subpart B) (see [HRPP policy 4.2](#)).
    - **4.2.3.** Prisoners (Subpart C) (see [HRPP policy 4.3](#)).
    - **4.2.4.** Children (Subpart D) (see [HRPP policy 4.4](#)).
    - **4.2.5.** Decisionally impaired (see [HRPP policy 4.6](#)).
    - **4.2.6.** Critically ill persons
    - **4.2.7.** Terminally ill persons
    - **4.2.8.** Blind or deaf persons, or persons with other disabilities
    - **4.2.9.** Economically or socially disadvantaged persons
    - **4.2.10.** Educationally disadvantaged persons
    - **4.2.11.** Employees and students (see [HRPP policy 4.7](#)).
    - **4.2.12.** Non-English speaking persons
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## 5.0 Additional Protections for Vulnerable Populations

- **5.1.** Investigators must consider whether subjects to be enrolled in their research might be vulnerable, and if so, what additional protections might be appropriate to provide additional protections.  
In making the latter determination, investigators should consider:

- **5.1.1.** Is inclusion of the vulnerable person or population necessary? That is, could the aims of the research be accomplished by enrolling persons or a population that is not (or less) vulnerable?

Note: Investigators should be aware that there are competing ethical imperative related to enrollment of vulnerable persons. The Belmont Principle of Respect for Persons requires that investigators protect those with limited autonomy (even to the extent of excluding them from the research); however, the Belmont Principles of Beneficence and Justice require that researchers provide the benefit of research, and distribute those benefits fairly.

Investigators should also be cognizant of the risks of not including certain populations in research. For example, considering children as research subjects, the National commission noted “The argument in favor of conducting research involving children rests on ... the consequences of not conducting research involving children in those instances. Such consequences might include the perpetuation of harmful practices, the introduction of untested practices, and the failure to develop new treatments ...” (National Commission: Research Involving Children. Report and Recommendations, 1977; page 21).

- **5.1.2.** If so, then are protections afforded to subjects adequate?
  - **5.1.2.1.** Do prospective subjects have difficulty providing voluntary, informed consent? Are condition for informed consent satisfied? (Is information presented in an understandable manner? Do subjects comprehend the details of the research and their rights as research subjects? Is the process of consent conducive to true voluntariness?)
  - **5.1.2.2.** Are prospective subjects at risk for exploitation?
- **5.2.** Specific additional protections that might be considered include (but are not limited to):
  - **5.2.1.** The use of an extended consent process.
  - **5.2.2.** The use of a consent monitor.
  - **5.2.3.** Appointment of a subject advocate.
  - **5.2.4.** Involvement of the subject’s family and/or friends.
  - **5.2.5.** The requirement for re-consenting of subjects/LARs.
  - **5.2.6.** Limits placed on risk.
  - **5.2.7.** Increased monitoring of the research through use of a Data Safety Monitoring Board or other mechanisms.
  - **5.2.8.** More stringent withdrawal criteria.
  - **5.2.9.** Longer study follow-up.
  - **5.2.10.** Exclusion from participating in the research.

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## **6.0 Investigator and IRB Procedures Regarding Inclusion of Vulnerable Persons or Populations**

- **6.1.** The investigator must identify whether research will include any population which is directly subject to the additional protections in 45 CFR 46 subpart B, C or D, or 21 CFR 56 subpart D
- **6.2.** The investigator must identify whether subject eligibility criteria will specifically target other potentially vulnerable populations, or whether there is a high likelihood that a sizable number of subjects will come from a vulnerable population.

Note: the intent here is to identify research proposals for which it would be reasonable to have additional protections in place prior to enrollment. The intent is not to identify situations when a vulnerable person would incidentally be enrolled. In the latter case, it is expected that the investigator would identify that person and take appropriate actions.

- **6.3.** The investigator must specifically describe additional protections for persons or populations identified in sections 7.1 and 7.2.
  - **6.4.** The IRB will consider whether inclusion of vulnerable subjects or populations is appropriate, and whether the additional protections proposed as adequate, as required in HRPP policy 2.5 (Criteria for Approval).
  - **6.5.** The IRB will consider whether the inclusion of vulnerable subjects satisfies the requirements of 45 CFR 46 subpart B, C or D, or 21 CFR 56 subpart D, and of HRPP policies 4.2 (Research Involving Pregnant Women, Human Fetuses, and Neonates – Nonviable or of Uncertain Viability), 4.3 (Research Involving Prisoners), 4.4 (Research Involving Children), 4.6 (Research Involving Subjects with Impaired Decision Making Capacity) and/or 4.7 (Research Involving Employees and Students).
  - **6.6.** If the IRB reviews and approves a protocol which does not involve vulnerable subjects but a subject, after enrollment, becomes vulnerable (for example, by being incarcerated, or becoming pregnant or homeless), the PI must notify the IRB and revise the IRB Application as applicable. The IRB will review the submission in order to determine that the vulnerable subject(s) has appropriate additional protections.
    - **6.6.1.** Subjects participating in federally funded research who fall under the requirements of Subparts B, C, or D must be withdrawn from the study unless their continued participation is in compliance with that Subpart.
    - **6.6.2.** The IRB determinations regarding inclusion of pregnant women, prisoners, and children will be documented in accordance with HRPP policies 2.2 (Full IRB Review), 2.3 (Expedited IRB Review), 4.2 (Research Involving Pregnant Women, Human Fetuses, and Neonates-Nonviable or of Uncertain Viability), 4.3 (Research Involving Prisoners), and/or 4.4 (Research Involving Children).
    - **6.6.3** The IRB determinations regarding inclusion of other vulnerable populations will be documented in accordance with HRPP policies 2.2 (Full IRB Review) and 2.3 (Expedited Review).
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## DOCUMENT HISTORY:

? Written: 1/6/2016 (Approved: 1/6/2016) - original author not recorded

? Revised: 1/26/2018 - revision not documented

# 4.2 Research Involving Pregnant Women, Human Fetuses, and Neonates (Nonviable or of Uncertain Viability)

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Last Revised: 9/25/2024

## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for IRB review and approval of research involving pregnant women, fetuses, and neonates (nonviable or of uncertain viability).

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## 2.0 Policy

It is the policy of the Organization that:

- 2.1. Federally funded non-exempt research involving pregnant women, fetuses, and neonates (nonviable or of uncertain viability) will be reviewed and approved in accordance with the requirements of HHS regulations at 45 CFR 46 Subpart B, and applicable state law.
  - 2.2. Other non-exempt research involving pregnant women, fetuses, and neonates (nonviable or of uncertain viability) will be reviewed and approved in accordance with equivalent protections. These protections will be based upon the ethical principles in the Belmont Report. In addition, the requirements in 45 CFR 46 Subpart B will be applied as appropriate in consideration of the nature of the research.
  - 2.3. Research involving fetuses and neonates (nonviable or of uncertain viability) will be reviewed and conducted in accordance with applicable state law.
  - 2.4. Women who are pregnant should not be routinely excluded from participating in research unless there are sound medical and/or scientific reasons not to include them. However, if pregnant women are justifiably excluded, the protocol must include a valid way to screen for pregnancy in accordance with [HRPP policy 3.10](#) (Pregnancy Testing).
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## 3.0 Definitions

- 3.1. 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.
  - 3.2. Fetus means the product of conception from implantation until delivery.
  - 3.3. Viable neonate means a neonate, after delivery, which can survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. (A viable neonate is covered by HHS regulations at 45 CFR 46, Subparts A and D).
  - 3.4. Nonviable neonate is a neonate after delivery that, although living, is not viable.
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## 4.0 IRB Review

In addition to review of research under HHS regulations at 45 CFR 46 (Subpart A) and FDA regulations at 21 CFR 50, 56 as applicable, the IRB must assure additional protections are in place for pregnant women, fetuses and/or neonates involved in research in accordance with the following:

- 4.1. Research involving pregnant women or fetuses
  - 4.1.1. For research which is subject to HHS regulations at 45 CFR 46 subpart B pregnant women may be involved in research if all of the following conditions are met.
    - 4.1.1.1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies involving non-pregnant women, have been conducted and provide data for assessing potential risks for the enrollment of pregnant women and fetuses.
    - 4.1.1.2. Any risk to the fetus is caused solely by interventions that offer direct benefit for the woman or fetus, OR if there is no prospect of direct benefit, the risk to the fetus must not be greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
    - 4.1.1.3. Any risk to the pregnant woman or the fetus is the least possible to achieve the research objectives.
    - 4.1.1.4. The consent of the pregnant woman alone is obtained when the research holds out (1) the prospect of direct benefit to the pregnant woman, (2) the prospect of a direct benefit both to the pregnant woman and the fetus, or (3) 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.
    - 4.1.1.5. The consent of both the pregnant woman and the father is obtained when the research holds out the prospect of direct benefit solely to the fetus. 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
    - 4.1.1.6. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
    - 4.1.1.7. For children who are pregnant assent of the pregnant minor and permission of the pregnant minor's parent(s) are obtained in accordance with



HHS regulations 45 CFR 46, Subpart D and HRPP policy 4.4 (Research Involving Children).

- 4.1.1.8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- 4.1.1.9. Individuals engaged in research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
- 4.1.1.10. Individuals engaged in research will have no part in determining the viability of a neonate.
- 4.1.2. For research which is not subject to HHS regulations at 45 CFR 46 subpart B pregnant women may be involved in research if all of the conditions in section 4.1.1 are met, with the following exceptions:
  - 4.1.2.1. The IRB may decide that preclinical studies on pregnant animals and clinical studies involving non-pregnant women are not reasonable requirements to protect subjects. For example, this requirement would likely be of limited value in social and behavioral science research, or minimal risk biomedical research.
  - 4.1.2.2. The IRB may decide that the purpose of the research need only be the development of knowledge which has sufficient value which justifies the enrollment of pregnant women.
  - 4.1.2.3. The IRB may decide that the consent of the father is not a requirement for research which holds out the prospect of direct benefit solely to the fetus.
- 4.2. Research Involving Neonates of Uncertain Viability
  - 4.2.1. Neonates of uncertain viability may only be involved in research if:
    - 4.2.1.1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
    - 4.2.1.2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
    - 4.2.1.3. Individuals involved in the research will have no part in determining the viability of the neonate.
    - 4.2.1.4. 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 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.
    - 4.2.1.5. 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, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.
  - 4.2.2. If a neonate of uncertain viability is determined, after delivery, to be viable, that neonate may be included in research only to the extent permitted by and in accord with the requirements of HHS regulations 45 CFR 46, Subpart D and HRPP policy 4.4 (Research Involving Children).
- 4.3. Research Involving Nonviable Neonates
  - 4.3.1. Nonviable neonates may only be involved in research if:
    - 4.3.1.1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

- 4.3.1.2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
  - 4.3.1.3. Individuals involved in the research will have no part in determining the viability of the neonate.
  - 4.3.1.4. The vital functions of the neonate will not be artificially maintained.
  - 4.3.1.5. The research will not terminate the heartbeat or respiration of the neonate.
  - 4.3.1.6. There is no additional risk to the neonate resulting from the research.
  - 4.3.1.7. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
  - 4.3.1.8. The legally effective informed consent of both parents of the neonate is required. 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.
    - 4.3.1.8.1. The waiver and alteration provisions at 45 CFR 46.116(e) and 45 CFR 46.116(f) do not apply.
    - 4.3.1.8.2. The consent of the father is not required where the pregnancy resulted from rape or incest.
    - 4.3.1.8.3. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate is not permitted.
  - 4.4. Research involving placenta, dead fetus(s) or fetal material
    - 4.4.1. Research involving the placenta, dead fetus, or fetal material after delivery does not constitute human subject research under 45 CFR 46 (unless any information associated with the material used in the research can be linked in any way to a living person). Research involving the placenta may occur if all federal, state, or local laws and regulations are met. Research involving dead fetus, or fetal material, is prohibited under University of Nebraska Board of Regents policies.
  - 4.5. Research not otherwise approvable
    - 4.5.1. Research which is subject to HHS regulations at 45 CFR 46 subpart B but which does not satisfy the requirements of 45 CFR 46 subpart B, and which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, may be conducted only if the additional requirements of 45 CFR 46.207 are met.
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## **5.0. Non-pregnant subjects who become pregnant during research**

- 5.1. If a subject becomes pregnant while actively participating in a research protocol, all research activities and interventions for the pregnant subject must stop until the protocol is reviewed under the requirements of this policy, except where the PI has determined that it is in the best interest of the pregnant subject to continue participating in the study and has provided justification to the IRB Chair who is authorized to make the final determination.
  - 5.1.1. If the investigator or the IRB chair determines that it is not in the best interest of the pregnant subject to remain in the study, participation will be terminated and the PI must make provisions for the continuation of any necessary treatment of the subject as appropriate.
  - 5.1.2. If the investigator and the IRB chair determines that it is in the best interest of the pregnant subject to continue participating, research activities may continue but

the study must be re-reviewed by the full IRB, as soon possible, in consideration of this policy.

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## **6.0 Documentation of Compliance with Subpart B**

- 6.1. For research reviewed by the convened IRB, compliance with Subpart B (or with the equivalent protections described in this policy) will be documented in the letter to the investigator which is part of the meeting minutes.
  - 6.2. For research reviewed through the expedited mechanism, compliance with Subpart B (or with the equivalent protections described in this policy) will be documented in the letter to the investigator which is available for review by the IRB in RSS.
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### **DOCUMENT HISTORY:**

? Written: 1/6/2016 (Approved: 1/6/2016) - original author not recorded

? Revised: 2/20/2018 - revision not documented

? Revised: 12/22/2022 – clarified exceptions to requirements under subpart B for research not subject to subpart B (section 4.1.2); deleted specific language related to 45 CFR 46.207 (section 4.5); stylistic changes for clarity.

? Revised: 9/25/2024 – added that research involving fetuses and neonates (nonviable or of uncertain viability) will be reviewed and conducted in accordance with applicable state law (section 2.3).

# 4.3 Research Involving Prisoners

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Last Revised: 01/17/2024

## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for review and approval of research involving prisoners.

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## 2.0 Policy

- 2.1. It is the policy of the Organization that federally funded research involving prisoners will be reviewed and approved in accordance with the requirements of 45 CFR 46 Subpart C.
  - 2.2. It is the policy of the Organization that for non-federally funded research involving prisoners, the Organization will apply equivalent protections. These protections will be based upon the ethical principles in the Belmont Report. In addition, the requirements in 45 CFR 46, Subpart C will be applied to the greatest extent possible in consideration of the nature of the research.
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## 3.0 Definitions

- 3.1. Prisoner is defined by HHS regulations at 45 CFR 46.303(c) 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 that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing."
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Note: In accordance with OHRP guidance, application of the regulatory definition of prisoner includes the following: 1) Individuals detained in a residential facility for court-ordered substance abuse treatment; or 2) Individuals with psychiatric illnesses that have been committed involuntarily to an institution as an alternative to criminal prosecution or incarceration.

Note: Individuals who are on probation or parole regardless of whether they are required to wear a monitoring device are generally not considered prisoners. Individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness are also not considered prisoners. However, such subjects are vulnerable and, therefore, must be afforded additional appropriate protections as required by 45 CFR 46.111(b).

- 3.2. Minimal risk in prisoner research is defined by HHS regulations at 45 CFR 46.303(d) as “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.”

Note: The IRB interprets the term “healthy persons” to mean the average healthy person in the general population who is not a prisoner.

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## 4.0 Additional IRB Requirements

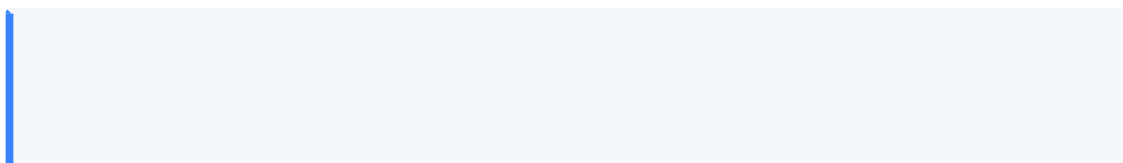
- 4.1. When reviewing research involving prisoners, the IRB will satisfy the following additional requirements:
  - 4.1.1. The majority of the members of the IRB will not have an association with the prison involved in the study (excluding the prisoner members).
  - 4.1.2. At least one member of the IRB will be a prisoner or a prisoner representative. The prisoner or prisoner representative must have a close working knowledge, understanding, and appreciation of prison conditions from the perspective of the prisoner.
- 4.2. A prisoner or prisoner representative must be involved in all IRB actions pertaining to protocols involving prisoners, including (but not limited to) a) initial review of the protocol, b) continuing review, c) protocol and/or consent changes, d) review of reports of unanticipated problems involving risks to subjects. When research involving prisoners is reviewed by the convened IRB the prisoner representative must be present as part of the

quorum and must present his/her review either orally or in writing.

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## 5.0 Permitted Research Involving Prisoners

- 5.1. In accordance with HHS regulations at 45 CFR 46.306(a)(2), research may involve prisoners as subjects only if the research falls under one or more of the categories listed below:
  - 5.1.1. Study of the possible causes, effects, and processes of incarceration and of criminal behavior, provided that the study presents no more than minimal risk, and no more than inconvenience to the subjects.
  - 5.1.2. Study of prisons as institutional structures, or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk, and no more than inconvenience to the subjects.
  - 5.1.3. 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 assault).
  - 5.1.4. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.
- 5.2. If HHS-funded research fits either category C or D above where prisoners are assigned to control groups which may not benefit from the research, final approval rests with the Secretary of HHS with OHRP acting on behalf of the Secretary. Following IRB approval, the entire research proposal (including the IRB-approved protocol, any relevant HHS grant application or proposal, consent documents, any IRB application forms, and any other information requested or required by the IRB for initial review) will be submitted to OHRP. OHRP will consult with appropriate experts, including experts in penology medicine and ethics, and publish notice, in the Federal Register, of intent to approve such research. HHS, through OHRP, will issue its approval in writing to the IRB.
- 5.3. For research which is not funded by HHS, neither certification to OHRP nor expert review for Categories C and D above is required. The IRB may however, at its discretion convene an equivalent expert review body to review studies classified under those categories.
- 5.4. Waiver of Requirements for Epidemiological Studies
  - 5.4.1. Epidemiologic studies involving prisoners as subjects need not meet the requirements of section 5.1, 5.2 and 5.3 of this policy provided:
    - 5.4.1.1. The sole purpose of the research is (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease.
    - 5.4.1.2. The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
    - 5.4.1.3. Prisoners are not a particular focus of the research.



Note: On June 20, 2003, HHS approved a waiver of the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for specified epidemiologic research conducted or supported by HHS. This means that the research under this waiver provision need not fall within the categories specified in Section 5.0 of this policy.

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## 6.0 Procedures for IRB Review of Research Involving Prisoners\*

- 6.1. If a research protocol will involve prisoners (per section 3.1 of this policy), the IRB application must also include completion of Addendum C: Research Involving Prisoners as Subjects.
- 6.2. The UNMC IRB will normally not use expedited review for protocols, changes, or continuing review of research involving prisoners.
- 6.3. The UNMC IRB does not allow exemption from IRB review of research involving prisoners.
- 6.4. The UNMC IRB does not allow monetary compensation of prisoners who serve as research participants.

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## 7.0 IRB Findings

- 7.1. The IRB will make the following additional findings for research involving prisoners (per 45 CFR 46.305(a)):
  - 7.1.1. The research represents one of the categories permissible under Section 5.0 of this policy.
  - 7.1.2. Any possible benefits 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.
  - 7.1.3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
  - 7.1.4. 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 subjects will be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
  - 7.1.5. The information is presented in language which is understandable to the subject population.
  - 7.1.6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.

- 7.1.7. If 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 prisoner' sentences and for informing participants of this fact.
  - 7.2. The IRB may grant a waiver or alteration of informed consent in accordance with HRPP policies 5.2 (Waiver or Alteration of Informed Consent and HIPAA Authorization).
  - 7.3. The IRB may grant a waiver of signed consent in accordance with HRPP policy 5.4 (Waiver of the Requirement to Obtain Signed Consent Form).
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## 8.0 Documentation of Compliance with Subpart C

- 8.1. For research reviewed by the convened IRB, compliance with Subpart C (or with the equivalent protections described in this policy) will be documented in the letter to the investigator which is part of the meeting minutes.
  - 8.2. If the IRB approves research involving prisoners funded by HHS that has been, the IRB will provide written certification to OHRP that it fulfilled the responsibilities described in this policy and in 45 CFR 46 subpart C. Specifically the certifications will include:
    - 8.2.1. The name and address of the institution.
    - 8.2.2. Identification of the research protocol and relevant HHS grant application or protocol.
    - 8.2.3. A copy of all paperwork necessary for IRB initial review (including detailed protocol, relevant HHS grant application or proposal, IRB application, ICF).
    - 8.2.4. Verification of the presence of a prisoner representative during consideration of the study.
    - 8.2.5. Verification of the required findings per section 7.1 of this policy, and 45 CFR 46.305(a).
    - 8.2.6. Determination that the research falls into one of the permitted categories of research per section 5.1 of this policy, and 45 CFR 46.306(a).
  - 8.3. For epidemiologic studies described in section 5.4 above funded by HHS, the IRB will provide written certification to OHRP as above, except that it will only verify that the requirements of 45 CFR 46.305(a)(2) through (7) were met.
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## 9.0 Special Circumstances

- 9.1. When a previously enrolled subject becomes a prisoner
  - 9.1.1. When a previously enrolled subject becomes a prisoner (as determined by the Executive Chair or designee, in consultation as appropriate with the prisoner representative) and the research was not reviewed and approved by the IRB in accordance with this policy, the PI must report the situation to the IRB immediately. All research activities and interventions for the now incarcerated prisoner-subject must stop until the protocol is reviewed under the requirements of this policy.
    - 9.1.1.1. If the investigator believes that it would be in the best interests of the subject to continue research activities while incarcerated, a request may be made to the IRB.
      - 9.1.1.1.1. If the research is NOT subject to the requirements of 45 CFR 46 subpart C then the IRB Executive Chair (or designee) may grant



temporary approval for the subject to continue in the study until the IRB has met and determined that all of the applicable requirements of this policy have been met. The IRB will be notified of the temporary approval at the next convened meeting.

- 9.1.1.1.2. If the research is subject to the requirements of 45 CFR 46 subpart C then the convened IRB (at either a scheduled meeting, or at a meeting of the RR-IRB) will review to determine whether requirements of 45 CFR 46 subpart C are met. The ORA will provide documentation of compliance with subpart C to OHRP as described in section 8.0 of this policy.
- 9.1.1.1.3. In either case, if some of the requirements of Subpart C or of this policy cannot be met, but it is in the best interests of the participant to continue the research intervention, the board may decide to keep the participant enrolled (and, if subject to subpart C, inform OHRP of the decision along with the justification), or may remove the participant from the study and keep them on the study intervention under an alternate mechanism such as compassionate use or off label use.
- 9.1.1.2. If the PI determines that the prisoner should be withdrawn from the study, the PI must make provisions for the continuation of any necessary treatment of the subject. In general, this would entail consultation with prison authorities and transfer of medical records. The IRB should be promptly notified of this subject's withdrawal and plans for continuity of treatment.
- 9.2. When a potential subject is an adolescent detained in a juvenile detention facility
  - 9.2.1. If a potential subject is an adolescent detained in a juvenile detention facility, the individual is both a child and a prisoner. In such a case additional protections for prisoners and children who are research subjects must be provided in accordance with this policy and HRPP policy 4.4 (Research Involving Children).
- 9.3. When the PI indicates that the proposed subject population may have a high risk of incarceration during the course of the study (but currently does not include prisoners)
  - 9.3.1. Any proposed subject population that has a high risk of incarceration during the course of the study is generally considered to be a vulnerable population. Therefore, the IRB must determine that there are appropriate additional protections in accordance with 45 CFR 46.111(b).

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## DOCUMENT HISTORY:

? Written: 4/14/2016 (Approved: 4/14/2016) - original author not recorded

? Revised: 2/19/2018 - revision not documented

? Revised: 12/10/2019 - revision not documented

? Revised: 01/17/2024 – specified that the prisoner representative review must be presented at a convened meeting either oral or written (section 4.2); clarified who makes determination whether an enrolled subject is a prisoner (section 9.1.1); clarified that executive chair or designee may provide temporary approval for a prisoner to continue only if research is not subject to 45 CFR 46 subpart C (section 9.1.1.1.1); clarified that convened IRB only may allow continuation of prisoner in research for research subject to 45 CFR 46 subpart C (section 9.1.1.1.2); clarified process if

convened IRB cannot find conditions of 45 CFR 46 subpart C met for already enrolled subject (9.1.1.1.3.); corrected numbering errors.

# 4.4 Research Involving Children

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## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for research involving children.

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## 2.0 Policy

It is the policy of the Organization that:

- **2.1.** Federally funded non-exempt research involving children will be reviewed and approved in accordance with the requirements of HHS regulations at 45 CFR 46 Subpart D; FDA regulations at 21 CFR 50 Subpart D (as applicable), and applicable state law. The IRB will classify the research in accordance with Subpart D and document how and why the proposal meets the requirements.
  - **2.2.** Other non-exempt research (non-federally funded research and non-FDA regulated) involving children will be reviewed and approved in accordance with equivalent protections. These protections will be based upon the ethical principles in the Belmont Report. In addition, the requirements in 45 CFR 46, Subpart D will be applied to the greatest extent possible in consideration of the nature of the research.
- 

## 3.0 Definitions

- **3.1.** Children: persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
  - **3.1.1.** In the state of Nebraska, the age of majority is defined, according to Nebraska State Statute 43-2101 as "all persons under nineteen years of age are declared to be minors, but in case any person marries under age of nineteen years, his or her minority ends."
  - **3.1.2.** If the subject is Native American living on federal tribal lands, regardless of the state law, federal law has set the age of majority at age 18.
  - **3.1.3.** If the research is conducted in another state under the oversight of the UNMC IRB, the age of majority is set by that state.
- **3.2.** Assent: a child's affirmative agreement to participate in research. Federal regulations and sound ethical practice require that assent be obtained when, in the judgment of the IRB in consultation with the investigator, the children are capable of providing assent.

Mere failure to object, absent affirmative agreement, is not construed as assent.

- **3.3. Commensurate:** the requirement that children are familiar with procedures that are reasonably similar in nature and risk proportional to those the child has experienced, or is expected to experience, and not restricted to specific situations the child has experienced.
- **3.4. Disorder or condition:** a specific (or set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.
- **3.5. Dissent:** a child's affirmative decision to decline participation in research.
- **3.6. Minimal risk:** "The probability and magnitude of harm or discomfort associated with the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." For the purpose of this policy "daily life" refers to the daily life of an average healthy child, not the daily life of the subject.

Note: The determination of minimal risk should take into account that a) children face differing risks at different ages, b) risks associated with repetitive tests may increase, and c) special/unique characteristics may make a certain population more vulnerable than average children (e.g., hemophilia). The risks associated with routine examinations or tests are equivalent to a routine well-child examination.

- **3.7. Minor increase over minimal risk:** a slight increase over minimal risk. Specifically "The increase in the probability and magnitude of harm is only slightly more than minimal risk. Any potential harms associated with the procedure will be transient and reversible in consideration of the nature of the harm (restricted to time of procedure or short post-experimental period). There is no or an extremely small probability that participants will experience as severe the potential pain, discomfort, stress, or harm associated with the procedure." (SACHRP 2005).
- **3.8. Vital importance:** There must be clear and significant scientific evidence that the interventions or procedures in the research are likely to yield generalizable knowledge that will contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration, or treatment of the subject's disorder or condition.
- **3.9. Parent:** a child's biological or adoptive parent.
- **3.10. Guardian:** an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. In Nebraska the governing statute is Neb Rev Stat 30-2627.
- **3.11. Permission:** the agreement (consent) of parent(s) or guardian(s) to the participation of the child or ward in research.
- **3.12. Ward (of the State):** a child who, as determined by the State where the child resides, is a foster child, is a ward of the State, or is in the custody of a public child welfare agency (92 NAC 51-003.67)

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## 4.0 Categories of Research

HHS and FDA regulations specify that research involving children must be approvable under one or more of the following four categories and meet the specified criteria. For the purposes of this policy, “IRB” refers both to the convened IRB and to an expedited reviewer as described in [HRPP 2.3](#) (Expedited Review).

- **4.1.** Research not involving greater than minimal risk (45 CFR 46.404; 21 CFR 50.51)
  - **4.1.1.** The IRB will determine and document (including protocol-specific information justifying each IRB finding) that the research presents no greater than minimal risk to children.
  - **4.1.2.** Adequate provisions must be made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408, 21 CFR 50.55, and Sections 5.0 and 6.0 of this policy.
- **4.2.** Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405; 21 CFR 50.52)
  - **4.2.1.** The IRB finds and documents (including protocol-specific information justifying each IRB finding) that more than minimal risk to children is presented by an intervention to procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject’s well-being.
  - **4.2.2.** The IRB finds that:
    - **4.2.2.1.** The risk is justified by the anticipated benefit to the subjects.
    - **4.2.2.2.** The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.
    - **4.2.2.3.** Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408, 21 CFR 50.55, and Sections 5.0 and 6.0 of this policy.
- **4.3.** 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; 21 CFR 50.53)
  - **4.3.1.** The IRB finds and documents (including protocol-specific information justifying each IRB finding) 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 subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject.
  - **4.3.2.** The IRB finds that:
    - **4.3.2.1.** The risk represents a minor increase over minimal risk.
    - **4.3.2.2.** The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
    - **4.3.2.3.** The intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition, which is of vital importance for the understanding or amelioration of the subjects’ disorder, or condition.
    - **4.3.2.4.** Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408, 21 CFR 50.55, and Sections 5.0 and 6.0 of this policy.
- **4.4.** 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; 21 CFR 50.54)

- **4.4.1.** The IRB will submit this category of research to HHS and/or FDA for approval, if the research is funded by HHS or is FDA regulated.
- **4.4.2.** In order to determine that the research should be submitted for review at the Federal level, the IRB must find and document the following:
  - **4.4.2.1.** The research does not qualify under 45 CFR 46.404, 405, 406; 21 CFR 50.51, 52, 53.
  - **4.4.2.2.** The research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children.
  - **4.4.2.3.** The research meets applicable requirements of 45 CFR 46; 46.408; 46.409; 21 CFR 50, 56, (as applicable).
  - **4.4.2.4.** Research will be conducted in accordance with sound ethical principles.
  - **4.4.2.5.** Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.
- **4.4.3.** If the research is not HHS-funded or subject to FDA regulations, the ORA will, at the IRB's discretion, convene an equivalent Local 407 Panel, as per HRPP policy 4.5 (Local 407 Panel Review of Pediatric Research).
- **4.5. Research Involving Wards**
  - **4.5.1.** HHS regulations at 45 CFR 46.409 and FDA regulations 21 CFR 50.56 have set specific requirements for children who have been declared wards of the state, other agency, institution or entity.
    - **4.5.1.1.** Wards may participate in research classified as 45 CFR 404 or 405 and 21 CFR 50.51 or 50.52 providing all of the requirements under Subpart D are met.
    - **4.5.1.2.** Wards may participate in research classified as 45 CFR 406 or 407 and 21 CFR 50.53 or 50.54 only if all of the following additional conditions are met:
      - **4.5.1.2.1.** The research is related to their status as wards or will be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.
      - **4.5.1.2.2.** An advocate will be appointed for each child who is a ward. The advocate must be approved by the IRB and fulfill the following requirements:
        - **4.5.1.2.2.1.** The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

Note: One individual may serve as an advocate for more than one child.

- **4.5.1.2.2.2.** The advocate must have appropriate education and training in order to take into consideration the nature of the research, the expectation of the advocacy role and the ability to act in the best interest of the child for the duration of the child's participation in the research.

Note: The advocate must have a) the ability to make a determination regarding each ward's participation in research that is independent and free of all conflicts of interest, b) ability to become familiar with the child's health, behavior, social and physical environment, and c) a willingness to serve an intermediary role between the child, investigator, guardians, and the IRB. This may include, as appropriate, meeting with wards, biological parents, foster parents, and investigators as necessary.

- **4.5.1.2.2.3.** The advocate must not be associated in any way with the research, the investigator(s) or the guardian organization, except in the role as advocate or a member of the IRB.
- **4.5.1.2.2.4.** The advocate must promptly notify the investigator and the IRB of any concerns about the child's participation in research.
- **4.5.2.** Children who are wards of the state or any other agency, institution, or entity, can be included in research only if the investigator demonstrates sufficient scientific justification for including this vulnerable population
- **4.5.3.** In the State of Nebraska, children who are wards of the state can be included in research only if the ward would receive direct treatment or therapy that might benefit him/her and Nebraska DHHS allows an exception to policy (390 NAC 11-002.04K).
- **4.5.4.** If a child becomes a ward while participating in the research, the IRB must be promptly notified and Request for Change submitted justifying the inclusion of Wards.

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## 5.0 Requirements for Parental Permission

- **5.1.** Permission (hereafter referred to as "consent") of the parent(s)/guardian(s) is required for research involving children unless one of the following:
  - **5.1.1.** The IRB determines that a research satisfies the criteria for a waiver of parental permission under 45 CFR 45.408(c); that is, the protocol 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), and provided further that the waiver is not inconsistent with federal, state, or local law.
    - **5.1.1.1.** If the IRB waives parental permission under 45 CFR 46.408(c) there must be an appropriate mechanism for protecting the children who will

participate as subjects in the research is substituted. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age maturity, status, and condition.

- **5.1.2.** The IRB determines that the research satisfies the criteria for a waiver of parental permission under the provisions of 45 CFR 46.116(f).

Note: As per “IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects (July 2017)”, FDA does not intend to object to an IRB approving a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 21 CFR 50.25, or waiving the requirements to obtain informed consent when the IRB makes the findings consistent with 45 CFR 46.116(f).

- **5.2.** The IRB shall determine, in accordance with and to the extent that consent is required, that adequate provisions are made for soliciting the permission of each child’s parents/guardians.
  - **5.2.1.** Consent of one parent/guardian is sufficient for research conducted under 45 CFR 46.404; 21 CFR 50.51, unless the IRB specifically finds that consent of two parents is necessary
  - **5.2.2.** Consent of one parent/guardian is required for research conducted under 45 CFR 46.405; 21 CFR 50.52, unless the IRB specifically finds that consent of two parents is necessary.
  - **5.2.3.** Consent of both parents/guardians is required for research conducted under 45 CFR 46.406; 21 CFR 50.53 unless one parent/guardian is deceased, unknown, incompetent, and not reasonably available or when only one parent/guardian has legal responsibility for the care and custody of the child.
  - **5.2.4.** Consent of both parents/guardians is required for research conducted under 45 CFR 46.407; 21 CFR 50.54 unless one parent/guardian is deceased, unknown, incompetent, not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child.
- **5.3.** Permission by parents/guardian must be documented in accordance with and to the extent required by 45 CFR 46.117 and 21 CFR 56.109
- **5.4.** Documentation of permission by parents/guardians may be waived if the IRB determines the conditions of 45 CFR 46.117(c); 21 CFR 56.109(c) are satisfied.

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## 6.0 Requirements for Child Assent

- **6.1.** The IRB will determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.
- **6.2.** The IRB believes that, in consideration of their cognitive ability and maturity, children younger than 7 years of age, as a group, cannot reasonably be involved in a formal process of assent. However, dependent upon the cognitive ability of an individual child the



investigator should engage that child in an appropriate discussion about participation in the research to the extent possible [45 CFR 46.408(a); 21 CFR 50.55(b)].

- **6.3.** Assent is required from children 7 to 18 years of age unless, the investigator provides justification for a waiver, and the IRB finds that:
    - **6.3.1.** The capacity of some, or all, of the children is so limited that they cannot be reasonably consulted. In making this determination the IRB shall take into account the ages, maturity, intellect, decision-making capacity, and psychological state of the children involved. This judgment may be made for all children involved in the research, a subset of children, or for each child as the IRB deems appropriate [45 CFR 46.408(a); 21 CFR 50.55(b)]. OR
    - **6.3.2.** The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research [45 CFR 46.408(c) and 21 CFR 50.55(c)]. OR
    - **6.3.3.** The research meets the requirements for a waiver of assent under 45 CFR 46.116(f); 21 CFR 50.55(d).
  - **6.4.** Unless assent has been waived as above, children who do not provide assent, or who actively dissent may not be enrolled in the research.
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## **7.0 Procedures for Child Assent**

- **7.1.** If a child is between the ages of 7 and 12 the following procedure for assent must be followed:
    - **7.1.1.** The child should be given a copy of the Child Information Sheet which includes a description of the research written at the appropriate language level. It should include (at least) the following: purpose, methods, risks, and the voluntary nature of participation.
    - **7.1.2.** The investigator should engage the child in an appropriate discussion about participation in the research to the extent possible in consideration of the child's age and cognitive ability. The child's parent(s) should be included in this discussion.
    - **7.1.3.** If the child agrees to participate, the investigator should document the child's assent in the research record.
  - **7.2.** If a child is between the ages of 13 and 18 the following procedure for assent must be followed:
    - **7.2.1.** The child should be given a copy of the Informed Consent Form.
    - **7.2.2.** The investigator should engage the child in an appropriate discussion about participation in the research. For younger children, it may be appropriate to include the child's parent(s) in this discussion.
    - **7.2.3.** If the child agrees to participate, assent should be documented by having the child sign the appropriate signature blank on the Informed Consent Form.
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## **8.0 Consent of Subjects Reaching the Age of Majority**

- **8.1.** Children who reach the age of majority while actively participating in an study must give their consent to continue participation in the research, at the first visit after reaching the legal age of majority in the manner described in IRB application. Subjects must then

sign the informed consent document as “subject” without parental co signature.

- **8.2.** If the study only involves data analysis (that is, all research interventions have been completed) children who reach the age of majority do not need to provide consent. However, it may be respectful to remind them of their participation in the research protocol.
  - **8.3.** If, upon reaching the age of majority, the now adult subject is unable to execute legally effective informed consent, the parental/legal guardian consent remains in effect. This must be documented in the study records or patient medical record and the IRB must be notified.
  - **8.4.** If, upon reaching the age of majority, the now adult subject refuses consent to continue participation in the study, no additional research interventions may be performed, and no additional data may be collected. Existing data collected under the parent/guardian consent process may still be used.
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## **9.0 Assent of Subjects Reaching the Age of 13 Years (Age of Written Assent)**

- **9.1.** Children who reach the age of written assent while actively participating in a study must give their written assent to continue participation in the research at the first visit after reaching that age if they are capable of providing assent. Assent will be obtained in the manner described in IRB application. Subjects must then sign an Informed Consent Form (which must also be signed by the parent or guardian).
  - **9.2.** If the study only involves data analysis (that is, all research interventions have been completed) children who reach the age of assent do not need to provide written assent.
  - **9.3.** If, upon reaching the age of written assent the subject is not capable of providing assent the parental/legal guardian consent remains in effect. This must be documented in the study records or patient medical record.
  - **9.4.** If, upon reaching the age of written assent, the subject refuses to provide written assent to continue participation in the study, no additional research interventions may be performed, and no additional data may be collected, unless the conditions of section 6.3 are met. Existing data collected under the parent/guardian consent process may still be used.
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## **10.0 Procedures for IRB Review**

- **10.1.** IRB Assignment:
  - **10.1.1.** The IRB-04 will review research that only involves children conducted within the Organization in accordance with the authority granted in HRPP policy 1.2 (Authority Granted to the IRB by the Organization).
  - **10.1.2.** The responsible IRB for research which includes both children and adults will be determined on a case-by-case basis by the IRB Executive Chair/designee. In general, protocols will be reviewed by the IRB-04 if the PI is: 1) a faculty member of the Department of Pediatrics or a pediatric subspecialty department or section (for example, Pediatric Anesthesia or Pediatric Surgery), or 2) a pediatrician or pediatric subspecialist with admitting privileges at CHMC. The IRB Executive Chair/designee, or the full IRB, may request appropriate consultation to assist in review of protocols

involving adults.

- **10.1.3.** In general, where the majority of subjects are adults but also include children, the research will be reviewed by IRB-01 or IRB-02.
  - **10.2.** IRB Review Process:
    - **10.2.1.** Applications which require review by the full IRB will be processed and reviewed in accordance with HRPP policy 2.2 (Full IRB Review).
    - **10.2.2.** Applications that are eligible for review by the expedited method will be processed and reviewed in accordance with HRPP policy 2.3 (Expedited Review).
    - **10.2.3.** The assigned IRB reviewer(s) for both expedited and full board reviews will utilize the Subpart D Addendum Checklist. Completion of the form is not required.
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## **11.0 Documentation of Compliance with Subpart D**

- **11.1.** For research reviewed by the convened IRB, compliance with Subpart D (or with the equivalent protections described in this policy) will be documented in the letter to the investigator which is part of the meeting minutes.
  - **11.2.** For research reviewed through the expedited mechanism, compliance with Subpart D (or with the equivalent protections described in this policy) will be documented in the letter to the investigator which is available for review by the IRB in RSS.
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### **DOCUMENT HISTORY:**

? Written: 1/6/2018 - original author not recorded

? Revised: 2/19/2018 - revision not documented

? Revised: 11/8/2022 - Deleted reference to Parental ICF; clarified that waiver of parental permission allowed under 2017 FDA guidance; added definition of ward per Nebraska Administrative Code; deleted pre 2018 Common rule citations; specified requirements to apply subpart D to non-exempt research only; clarified that "IRB" refers to convened IRB and to expedited reviewer; deleted reference to Youth Information sheet; clarified that Youth signs the appropriate signature blank on the ICF; clarified age 13 as "age of written assent" (rather than "age of assent") {section 9.0}; clarified process of written assent upon reaching age 13.

# 4.5 Local 407 Panel Review of Pediatric Research

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## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for convening a local 407 Panel to consider pediatric research which is not federally funded or FDA regulated.

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## 2.0 Policy

It is the policy of the Organization that research involving minors which is neither funded by HHS nor regulated by FDA, and which presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children but does not meet the requirements of HHS regulations at 45 CFR 46.404, 46.405, or 46.406 may be reviewed by a local 407 panel.

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## 3.0 Definitions

- **3.1. *Children*** are defined as persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. See [HRPP policy 4.4](#) (Research Involving Children), section 3.1] for additional details.
- 

## 4.0 Eligibility for Local 407 Panel Review

- **4.1.** The Executive Chair or the Chair IRB-04 (Joint Pediatric IRB) may convene a local 407 Panel if all of the following conditions are met:
  - **4.1.1.** The research neither funded by HHS nor regulated by FDA; and
  - **4.1.2.** The IRB determines, by two-thirds majority vote, that:
    - **4.1.2.1.** A research protocol presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and
    - **4.1.2.2.** The IRB does not believe the research meets the requirements of HHS regulations at 45 CFR 46.404, 46.405, or 46.406.

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## 5.0 Local 407 Panel Membership

- **5.1.** The local 407 Panel will include at least 5 voting members and 1 non-voting member:
    - **5.1.1.** Two or more members in a discipline relevant to the research being reviewed. At least one must be unaffiliated with the institution.
    - **5.1.2.** Two or more members with general pediatrics experience. If possible, these members will have been present at the IRB-04 meeting during which the protocol was previously reviewed.
    - **5.1.3.** One non-scientist
    - **5.1.4.** The IRB Executive Chair or the Chair of IRB-04 will serve as the Chair of the local 407 panel, and will be non-voting
  - **5.2.** If a member with the expertise in a discipline relevant to the research being reviewed is not available locally, then the IRB Executive Chair will enlist the services of a non-local consultant. The consultant will receive the materials described below and will provide a written response to the general and specific questions noted below for consideration by the Panel.
  - **5.3.** The role of the Local 407 Panel Chair will be to:
    - **5.3.1.** Chair the meeting and focus relevant discussion.
    - **5.3.2.** Provide relevant regulatory information and guidance to the 407 Panel to assist their analysis.
    - **5.3.3.** Present a summary of the research.
    - **5.3.4.** Present the analysis of the IRB with respect to classification under 45 CFR 46.404, 405, and 406.
    - **5.3.5.** Answer questions from the panel relevant to the deliberations of the IRB.
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## 6.0 407 Panel Review

- **6.1.** Prior to the Local 407 Panel Review, the investigator will be informed the panel will be convened and will be given the opportunity to present written comments to the Panel in support of the criteria described in section 6.4B and 6.4C below (that is, 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 the research will be conducted in accordance with sound ethical principles).
- **6.2.** The following materials will be distributed to the 407 Panel members, at least one week prior to the meeting:
  - **6.2.1.** A copy of the IRB application, full protocol, ICF and information sheet, and all other relevant protocol related documents.
  - **6.2.2.** Any relevant questions for consideration.
  - **6.2.3.** Any additional written materials provided by the investigator
- **6.3.** At the scheduled Local 407 Panel meeting, the Chair will present a summary of the research, followed by the analysis of the IRB with respect to the classification under 45 CFR 46.404, 405, and 406.
- **6.4.** The Local 407 Panel will determine whether the research satisfies the following criteria:
  - **6.4.1.** The research does not meet the requirements of 46.404, 405 or 406; and
  - **6.4.2.** 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
  - **6.4.3.** The research will be conducted in accordance with sound ethical principles
  - **6.5.** Recommendations from the Panel whether the research satisfies the criteria in section 6.4 above will be made based on a simple majority vote. The Panel may also comment, as a group or individually, on the specific criteria in section 6.4.
  - **6.6.** The recommendations of the Local 407 Panel, including individual comments and findings, will be transmitted to the full IRB.
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## 7.0 Full IRB Review

- **7.1.** At its subsequent convened meeting, the IRB will re-review the research, utilizing the findings of the Local 407 Panel in its deliberations, and make one of the following determinations:
    - **7.1.1.** The research, in fact, satisfies the regulatory criteria for approval under HHS regulations at 45 CFR 46.404, 405, or 406.
    - **7.1.2.** The research satisfies the criteria for approval under 45 CFR 46.407; specifically:
      - **7.1.2.1.** The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
      - **7.1.2.2.** The research will be conducted in accordance with sound ethical principles; and
      - **7.1.2.3.** Adequate provisions have been made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.
    - **7.1.3.** The research is not approved.
  - **7.2.** A two-thirds majority vote will be required to approve the research under section 7.1.1 or 7.1.2 above. If a two-thirds majority vote is not obtained then the research is not approved.
  - **7.3.** The investigator will be informed, in writing, of the decision of the IRB promptly after the meeting of the convened IRB.
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# 4.6 IRB Review of Research Involving Subjects with Impaired Decision-Making Capacity

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## 1.0 Purpose

The purpose of this policy is to describe the Organization's requirements for IRB review of research involving subjects who have impaired decision-making capacity.

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## 2.0 Policy

It is the policy of the Organization that research involving subjects who have impaired decision-making capacity must include appropriate additional protections in accordance with the ethical principles described in the Belmont Report, and the requirements of 45 CFR 46.111(b) and 21 CFR 56.111(b), as applicable.

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## 3.0 Definitions

- 3.1. Decisionally impaired person, in the context of human subject research, means an adult with diminished capacity for judgment and reasoning such that they are unable to make an informed, voluntary decision to participate in research. The impairment which leads to this diminished capacity may be a temporary acute condition, may fluctuate, or may be a more long-term or permanent condition. It may be the result of any psychiatric disorder, an organic impairment, a developmental disorder, or severe acute illnesses associated with cognitive impairment.

Note: Capacity, defined as an individual's ability to make an informed decision, should not be confused with competence. Competence is a legal state, adjudicated by a court.



- 3.2. Legally Authorized Representative (LAR) is defined as “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation ... in research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject ...” (45 CFR 46.102(i)). “Legally authorized representative” in the context of research is not defined in the Nebraska revised statutes.

Note: OHRP Guidance states that “In these states [that have no law specifically addressing the issue of consent in the research context], law that addresses who is authorized to give consent on behalf of another person to specific medical procedures or generally to medical treatment may be relevant if the research involves those medical procedures or medical treatment. When the laws of the jurisdiction in which the research is being conducted provide a reasonable basis for authorizing an individual to consent on behalf of a prospective subject to their participation in the research procedure(s), OHRP would consider such an individual to be an LAR as defined by HHS regulations at 45 CFR 46.102(c).”

- 3.2.1. Under Nebraska law, the following persons may serve as a Legally Authorized Representative
  - 3.2.1.1. Parents and guardians having legal custody of the decisionally impaired person.
  - 3.2.1.2. The court-appointed legal guardian of the decisionally impaired person in accordance with Neb. Rev. Stat. 30-2627.
  - 3.2.1.3. The individual authorized to consent on behalf of a decisionally impaired person pursuant to a legally effective Health Care Power of Attorney (POA-HC).
- 3.2.2. In addition, Institutionally Authorized Surrogate (IAS), as defined below, may serve as a LAR for the purpose of this policy, except the IAS may not provide consent (permission) for category 3 research, as discussed below.
- 3.3. Institutionally Authorized Surrogate (IAS) is defined as a person authorized by the Organization to provide consent for medical procedures and tests for a patient who lacks capacity, and for whom there is not an LAR under Nebraska law. Persons who may act as IAS, and the priority order of such persons, are described in Nebraska Medicine policy MS14 (Consents and Permits) and/or Children’s Nebraska policy (Consent for Treatment) as applicable.
- 3.4. Adult assent is defined as the affirmative agreement of a decisionally impaired person to participate in research.
- 3.5. Dissent is defined as an objection to participation. In general, dissent is considered meaningful if it is unequivocal or sustained after an effort to relieve concerns and/or distress (Black B, et al; Am J Geriatr Psychiatry 18(1), 77-85, 2010)

## 4.0 Assessment of Capacity to Consent



- 4.1. The determination that a prospective subject is decisionally-impaired and, therefore, lacks the capacity to provide legally effective informed consent may have been a) adjudicated by the Court, or b) determined by an investigator, who, by their professional training, licensure, or experience, is qualified to determine capacity, or c) determined by an independent assessor.
  - 4.2. The method utilized to determine capacity may vary depending on the characteristics of the research protocol (including the risks and the risk-benefit relationship) and of the subject population. In general, with increasing risks, less favorable risk-benefit relationship, expected higher proportion of decisionally-impaired subjects, or expected greater depth of impairment, the assessment of capacity should utilize more formal tools. Standard tools include, but are not limited to:
    - 4.2.1. Clinical interviews
    - 4.2.2. Mini-Mental Status Exam (MMSE)
    - 4.2.3. “Assessment of Capacity to Consent to Participate in Research” instrument available on the IRB website
    - 4.2.4. MacArthur Competency Assessment Tool for Clinical Research (MacCat-CR)
  - 4.3. For research studies involving higher risks, less favorable risk-benefit relationship, expected higher proportion of decisionally-impaired subjects, or expected greater depth of impairment, the investigator should consider the use of an independent, experienced assessor and/or an independent monitor of the consent/assent process.
  - 4.4. Researchers should reassess capacity for individuals who exhibit fluctuating capacity levels, or if the research involves a population where it would be reasonably expected that capacity would be regained for at least some of the subjects.
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## **5.0 Appointment and Authority of the LAR or IAS**

- 5.1. If an individual lacks the capacity to consent, they can be enrolled in research only if an LAR provides consent (permission) on their behalf.
  - 5.2. If a prospective subject does not have an LAR as defined above, an IAS should be identified.
  - 5.3. The prospective subject’s capacity to choose an IAS should be assessed and, when possible, the subject’s choice should be honored.
  - 5.4. Availability, willingness and capacity to serve as a responsible surrogate decision-maker should be considered in the appointment of an IAS.
  - 5.5. The LAR or IAS should normally use “substituted judgment” where possible as opposed to “best interests”. It is important for the LAR or IAS to consider what would be the subject’s position given a choice whether or not to participate in the research when they were not cognitively impaired.
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## **6.0 Assent and Dissent**

- 6.1. The investigator must make adequate provisions for soliciting the assent of decisionally-impaired persons, when in the judgment of the investigator and the IRB they are capable of providing assent.
- 6.2. If the investigator and the IRB determine that the capability of some or all of the potential subjects of the research is so limited that they cannot reasonably be consulted or

that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the potential subjects and is available only in the context of the research, the assent of the decisionally-impaired persons is not a necessary condition for proceeding with the research.

- 6.3. If a decisionally-impaired person exhibits unequivocal or sustained dissent to initially participate in research, that dissent must be honored as long as the research does not hold out the prospect of direct subject benefit that is only available in the context of the research.
    - 6.3.1. If the research holds the prospect of direct subject benefit, approval to override the decisionally impaired person's dissent and enroll the individual in the research must be obtained from the IRB Executive Chair. The full IRB will be notified of the IRB Executive Chair's decision, and the board has the authority to accept the IRB Executive Chair's decision, require additional actions, or require withdrawal of the subject.
  - 6.4. If a decisionally impaired person exhibits unequivocal or sustained dissent while participating in research, that dissent must be honored as long as the research does not hold out the prospect of direct subject benefit that is only available in the context of the research. If the research holds the prospect of direct subject benefit, approval to override the decisionally impaired person's dissent and continue the subject's participation in the research must be obtained from the IRB Executive Chair or designee. The full IRB will be notified of the approval, and the board has the authority to accept the approval, require additional actions, or require withdrawal of the subject
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## **7.0 Acceptable Research Involving Decisionally Impaired Subjects**

- 7.1. Category 1 - Minimal risk: A decisionally impaired subject may participate in research involving minimal risk with no direct subject benefit if an LAR or IAS provides consent, and the decisionally impaired person provides assent (as described above).
- 7.2. Category 2 – Greater than minimal risk with the prospect of direct benefit: A decisionally impaired subject may participate in research involving greater than minimal risk and a prospect of direct benefit if:
  - 7.2.1. The risk-benefit relationship is favorable, and
  - 7.2.2. The risk-benefit relationship is at least as favorable as available alternative therapies, and
  - 7.2.3. An LAR or IAS provides consent, and the decisionally impaired person provides assent (as described above).
- 7.3. Category 3 - Greater than minimal risk with no prospect of direct benefit: A decisionally impaired subject may participate in research involving greater than minimal risk without prospect of direct benefit only if:
  - 7.3.1. The research represents only a minor increase over minimal risk, and
  - 7.3.2. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual medical, dental, psychological, social, or educational situations; and
  - 7.3.3. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

- 7.3.4. An LAR provides consent, and the decisionally impaired person provides assent (as described above).

Note: an IAS is not authorized to provide consent for category 3 research.

- 7.4. Cognitively impaired persons may not be enrolled into research which does not fall into one of the above 3 categories.
- 7.5. Cognitively impaired persons who are under a court mandated therapy for a psychiatric disorder are not eligible to participate in research.

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## 8.0 Additional Protections

In consideration of the characteristics of the subject population, the nature of the research and the risk level, the IRB will determine what additional protections are necessary. Additional protections for vulnerable subject populations which include individuals who are decisionally impaired are described in HRPP policy 4.1 (Additional Protections for Vulnerable Populations).

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## 9.0 IRB Review

- 9.1. Applications which require review by the full IRB will be processed and reviewed in accordance with HRPP policy 2.2 (Full IRB Review). In consideration of the nature of the protocol, one or more IRB members who are knowledgeable about or experienced in working with decisionally impaired persons will be involved in the review. As necessary, a consultant will be appointed to assist the IRB in their review.
- 9.2. Applications that are eligible for review by the expedited method will be processed and reviewed in accordance with HRPP policy 2.3 (Expedited Review). In consideration of the nature of the protocol, one or more IRB members who are knowledgeable about or experienced in working with decisionally impaired persons will be involved in the review. As necessary, a consultant will be appointed to assist in the expedited review.
- 9.3. The IRB will determine:
  - 9.3.1. Whether the research is allowable as above (“Acceptable Research Involving Decisionally Impaired Subjects”); and
  - 9.3.2. Whether there are adequate additional protections for vulnerable populations; and
  - 9.3.3. Whether assent and dissent will be managed as per requirements above (“Assent and Dissent”); and
  - 9.3.4. Whether capacity is being assessed adequately; and
  - 9.3.5. Whether there are adequate plans for re-consent or withdrawal should a subject regain capacity.

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## 10.0 Disclosure and Consent for Continuing Participation

If a person with diminished capacity regains capacity during the conduct of the research, they must be fully informed about the research and the circumstances of their enrollment. Their consent to continue in the research protocol must be obtained in accordance with [HRPP policy 5.1](#) (Obtaining Informed Consent from Research Subjects).

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## 11.0 Disclosure After the Research has Been Completed

If a person with diminished capacity regains capacity following completion of the conduct of the research, they must be fully informed about the research and the circumstances of their enrollment.

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## 12.0 Consent Forms/Information Sheet

- 12.1. Informed consent (permission) of the LAR or IAS will be documented in accordance with [HRPP Policy 5.1](#) (Obtaining Informed Consent from Research Subjects).
  - 12.2. As appropriate, subjects with impaired decisional making capacity will be provided with an Information Sheet. The Information Sheet should be written in simple language aimed at the appropriate cognitive level of the decisionally impaired subjects to be enrolled in the study. The Information sheet should contain the elements of assent that are found in the Information Sheet Template.
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? Written: 1/20/2016 (Approved: 1/20/2016) - original author not recorded

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? Revised: 12/8/2022 - Revised definition of LAR as per 45 CFR 46.102(i); deleted reference to pre-2018 Common Rule; defined IAS and clarified priority order of IAS by referencing Nebraska Medicine policy MS14; defined dissent; deleted reference to LAR ICF.

? Revised: 11/27/2024 - modified definition of capacity to remove extraneous language; revised "Cognitively impaired" to "decisionally impaired"; added reference to Children's Nebraska policy (Consent for Treatment); stylistic and other minor changes.

# 4.7 Research Involving Employees of the Organization and Students as Subjects

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## 1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for IRB review and approval of research involving employees of the Organization, and/or students as subjects. These persons are considered vulnerable because of the potential for undue influence or coercion.

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## 2.0 Policy

- **2.1.** It is the policy of the Organization that students, and employees of the Organization, may be recruited for research participation. To the extent that these subjects are vulnerable, the research plan must include additional safeguards to protect the rights and welfare of these subjects.
  - **2.2.** It is the policy of the Organization that the recruitment of employees working directly for, or under the supervision of, the PI or other study personnel, is discouraged.
  - **2.3.** It is the policy of the Organization that the recruitment of students taking classes from the PI or other study personnel, is discouraged.
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## 3.0 Students as Research Participants

- **3.1.** Students (for example, undergraduates, graduate students, medical students, residents, fellows, doctoral students) may be recruited for research participation.
- **3.2.** A student may not be required to participate in research without a comparable non-research alternative offered as a course requirement.
- **3.3.** Students (individuals or groups) should not be selected solely on the basis of convenience when they would not otherwise be appropriate for inclusion
- **3.4.** Recruitment of students taking classes from the PI or other study personnel is strongly discouraged; when such recruitment is scientifically justified and important to the conduct of the research, there must be additional safeguards in place to reduce the risk of undue influence or coercion.

- **3.5.** A student's decision about research participation may not affect grades or other such assessments of opportunities for the student.
  - **3.6.** Attention must be paid by the investigator to the risks to the student's privacy, since the classroom situation may make it difficult to keep an individual's participation confidential
  - **3.7.** Use of student education records for research must comply with the requirements of the Family Educational and Rights Privacy Act (FERPA) at 34 CFR 99
  - **3.8.** Research involving surveys with students in elementary and secondary schools that receive funding from the Department of Education must also comply with the Protection of Pupil Rights Amendment (PPRA) at 34 CFR 98.
  - **3.9.** UNO Students may participate in the SONA Research Participation System. All preceding requirements must be met. Any other student database or registry used for recruitment purposes must have procedures in place to exclude students that have enacted a FERPA hold on their registry information.
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## **4.0 Research Involving Employees of the Organization as Research Participants**

- **4.1.** Employees (full-time, part time or student) of the Organization may be recruited for research participation.
  - **4.2.** An employee may not be required to participate in research as a condition of employment.
  - **4.3.** Employees should not be selected solely on the basis of convenience when they would not otherwise be appropriate for inclusion
  - **4.4.** Recruitment of employees under the supervision of the PI or other study personnel is strongly discouraged; when such recruitment is scientifically justified and important to the conduct of the research, there must be additional safeguards in place to reduce the risk of undue influence or coercion.
  - **4.5.** An employee's decision about research participation may not affect performance evaluations or other such assessments or opportunities for the employee.
  - **4.6.** Attention must be paid by the investigator to the risks to the employee's privacy, since the workplace situation may make it difficult to keep an individual's participation confidential
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## **5.0 IRB Review**

- **5.1.** Research involving employees of the Organization, or students may be reviewed by the full convened IRB (as per HRPP policy 2.2) or using an expedited procedure (as per HRPP policy 2.3). The IRB application must clearly address:
  - **5.1.1.** Justification of the need to recruit the particular subject population
  - **5.1.2.** A description of any additional safeguards have been included in the study to protect the rights and welfare of these subjects.
- **5.2.** If an investigator proposes to recruit employees working for, or under the supervision of, the PI or other study personnel; or students taking classes from the PI or other study

personnel, the IRB application must clearly address:

- **5.2.1.** The nature of the professional relationship.
  - **5.2.2.** Justification of the need to recruit the particular subject population. This justification must be particularly strong for any study which involves greater than minimal risk procedures.
  - **5.2.3.** The plan for minimizing the risk of undue influence and/or coercion is the process of recruitment and consent.
  - **5.2.4.** A description of any additional safeguards have been included in the study to protect the rights and welfare of these subjects.
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