4.4 Research Involving Children

1.0 Purpose

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

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)

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 the 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.

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.

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.

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.

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.

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.

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.

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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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. {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

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