1.0 Purpose
The purpose of this policy and procedure is to describe the Organization’s requirements for research involving children.

2.0 Policy
It is the policy of the Organization that additional protection for children involved in research 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.

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.

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.”

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.

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 is defined as 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, the children are capable of providing assent. Mere failure to object, absent affirmative agreement, is not construed as assent.

3.3 Commensurate is defined as the requirement that children and/or their parents/guardians 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 is defined as 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 is defined as a child’s affirmative decision to decline participation in research.

3.6 Minimal risk means "The probability (of occurrence) and magnitude (seriousness) of harm or discomfort (e.g., psychological, social, legal, economic) associated with the research are not greater than those ordinarily encountered in daily life (of the average child in the general population) or during the performance of routine physical or psychological examinations or tests.” Minimal risk, therefore, is used to define a threshold of anticipated harm or discomfort associated with the research that is low.
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** is defined as a slight increase over minimal risk. In determining whether the research procedures or interventions present a minor increase over minimal risk, the IRB will consider the following criteria: 1) magnitude, probability, and duration of the potential harm in consideration of the characteristics of the subject population and 2) irreversibility of the harm to the child.

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** is defined as a child’s biological or adoptive parent.

3.10 **Guardian** is defined as 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** is defined as the agreement (consent) of parent(s) or guardian(s) to the participation of the child or ward in research.

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 (4) categories and meet the specified criteria:

4.1 **Research not involving greater than minimal risk (45 CFR 46.404; 21 CFR 50.51)**

A. The IRB will determine and document (including protocol-specific information justifying each IRB finding) that no greater than minimal risk to children is presented.

B. 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)**

A. 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.

B. The IRB finds that:

1) The risk is justified by the anticipated benefit to the subjects.

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.
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)**

A. 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.

B. The IRB finds that:

1) The risk represents a minor increase over minimal risk.

2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.

3) 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) 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)**

A. 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. If the research is not HHS-funded or subject to FDA requirements, the IRB will, at the Board’s discretion, convene an equivalent expert review panel.

B. In order to determine whether the research should be submitted for review at the Federal level, the IRB must find and document the following:

1) The research does not qualify under 45 CFR 46.404, 405, 406; 21 CFR 50.51, 52, 53.

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.

3) The research meets applicable requirements of 45 CFR 46; 46.408; 46.409; 21 CFR 50, 56, (as applicable).

4) Research will be conducted in accordance with sound ethical principles.

5) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.
4.5 Research Involving Wards

A. 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.

B. 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.

C. 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:

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.

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:

   a) 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.

   b) 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.

   c) 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.

   d) The advocate must promptly notify the investigator and the IRB of any concerns about the child’s participation in research.

D. The enrollment of wards in the research is justified and permitted by Nebraska State Law. Children, who are wards of the state or any other agency, institution, or entity, can be included in research only if there is sufficient justification for including this vulnerable population. In the state of Nebraska Department wards are not permitted to participate in research unless the Department allows an exception.

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 a waiver is granted by the IRB under the provisions of 45 CFR 46.408(c) or 45 CFR 46.116(d).
A. In addition to the provisions for waiver, if the IRB determines that a research 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), it may waive the consent requirements, provide an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, ad provide further that the waiver is not inconsistent with federal, state, or local law.

B. 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.

Note: Waiver of parental consent is not applicable for FDA regulated research.

5.2 Permission by parents or guardian must be documented in accordance with and to the extent required.

5.3 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 or guardians.

5.4 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.

5.5 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.

5.6 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.

5.7 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.

5.8 The IRB requires utilization of a Parental/Guardian Consent Form written in accordance with the IRB template.

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 given age, maturity, intellect, decision-making capacity and psychological state, 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 justifies a waiver of assent in Addendum L in accordance with the following:

A. The IRB is able to determine that 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

B. The IRB is able to determine that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research [45 CFR 46.408(c) and 21 CFR 50.55(c)]. OR

C. The IRB is able to determine that the research meets the requirements for a waiver of assent under 45 CFR 46.116(d); 21 CFR 50.55(d).

D. Unless assent has been waived as above, children who do not provide assent, or who actively dissent may not be enrolled in the research.

E. Even where the IRB determines that the subjects are capable of assenting the IRB may still waive the assent requirement under circumstances in which consent may be waived.

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:

A. The child should be given a copy of the Child Study 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.

B. 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.

C. 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:

A. The child should be given a copy of the Youth Study Information Sheet which includes a description of the research written at the appropriate language level. It should include (at least) the elements of assent specified in Section 7.1(A) above.

B. 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.

C. If the child agrees to participate, assent should be documented by having the child sign the assent signature blank on the parental 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 IRB-approved study must be given 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 IRB-approved adult informed consent document.

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.

The now adult subject has the right to refuse to continue participation in the study. This is to be respected and undue pressure or coercion to continue may not be applied. While new data may not be collected on subjects refusing participation, existing prior data collected under the parent/guardian consent process can be used.

9.0 Waiver or Alteration of Parental Consent and/or Child Assent

9.1 If the IRB application includes a request for waiver/alteration of parent consent or child assent, the following addenda must be completed (as applicable) [45 CFR 46.408(c); the HIPAA Privacy Rule; 45 CFR 46.116(d)]:

A. *Addendum J: Waiver or Alteration of Informed Consent and HIPAA Authorization in Biomedical, Medical Records, HBM Research, Biorepositories, and Data Banking*

B. *Addendum K: Waiver or Alteration of Informed Consent and HIPAA Authorization in Social Science and Behavioral Research*

C. *Addendum L: Waiver or Alteration of Child Assent*

9.2 A waiver of parental/guardian consent is *not* permitted in FDA regulated research.

10.0 Waiver for the Requirement for Documentation of Parental Consent

10.1 If the IRB application includes a request for waiver of the requirement to obtain a signed consent, *Addendum M: Waiver of Requirement to Obtain Signed Consent* must be included [45 CFR 46.117(c); 21 CFR 56.109(c).]

11.0 Procedures for IRB Review

11.1 *IRB Assignment:*

A. The Joint Pediatric IRB (PedsIRB) will review research involving only children (less than 19 years of age) conducted within the Organization in accordance with the authorization specified in *HRPP policies #1.2.*

B. The responsible IRB for research which includes both children and adults will be determined on a case-by-case basis by the IRB Chair/designee. In general, protocols will be reviewed by the PedsIRB 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 CH&MC. The IRB Chair/designee, or the full PedsIRB, may request appropriate consultation to assist in review of protocols involving adults.
C. In general, where the majority of subjects are adults but also include older children (i.e., adolescents), the research will be reviewed by IRB-01 or IRB-02.

11.2 **IRB Application Submission Requirements:**

A. For research involving only children, the investigator must submit the IRB application for *Pediatric Biomedical Research* or *Pediatric Social Science and Behavioral Research*.

B. For research including both children and adults which will be reviewed by the PedsIRB (per Section 11.1 above), the investigator must submit the 1) *Pediatric Biomedical Research* or *Pediatric Social Science and Behavioral Research*, and 2) *Addendum Y: Research Involving Adults*.

C. For research where the majority of subjects are adults but also include adolescents or young adults under review by IRB-01 or IRB-02 (per Section 11.1 above), the investigator must submit: 1) the IRB Application for *Biomedical Research* or *Social Science and Behavioral Research*, and 2) *Addendum D: Research Involving Children*.

D. If the research includes children who are wards of the state or any other agency, institution, or entity, the IRB application must also include *Addendum H: Research Involving Children Who Are Wards*. If the investigator may reasonably anticipate that some subjects may become wards during the course of research which provides a vitally important therapeutic option, the above addendum should be submitted.

E. If a child becomes a ward while participating in the research, the IRB must be promptly notified and *Addendum H* should be submitted.

11.3 **IRB Review Process:**

A. Applications which require review by the full IRB will be processed and reviewed in accordance with *HRPP policy #2.2*.

B. Applications that are eligible for review by the expedited method will be processed and reviewed in accordance with *HRPP policy #2.3*.

C. 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.

12.0 **Documentation of Compliance with Subpart D**

12.1 IRB review and approval of research involving children must include all necessary documentation that the research meets the additional requirements of 45 CFR 46, Subpart D; 21 CFR 50, Subpart D (as applicable); and applicable HRPP policies.

12.2 Research qualifying for a waiver or alteration of parental/guardian consent/child assent must be documented in accordance with applicable requirements of 45 CFR 46.116(d), HIPAA Privacy Rule, or 45 CFR 46.408(c). FDA-regulated research does not qualify for a waiver of parental/guardian consent. Documentation will include a copy of the IRB-approved *Addendum L*.

12.3 Research qualifying for a waiver of the requirement for the investigator to obtain a signed consent form must be documented in accordance with applicable requirements
of 45 CFR 46.117(c); 21 CFR 56.109(c), (d). Documentation will include a copy of the IRB-approved Addendum M.

**Administrative Approval:**
Ernest D. Prentice, PhD.  Associate Vice Chancellor for Academic Affairs and Institutional Official
Bruce G. Gordon, MD    IRB Executive Chair