

RESEARCH INVOLVING SPECIAL POPULATIONS: CHILDREN

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THIS POLICY PERTAINS TO:			ALL RESEARCH SUBMITTED TO THE IRB				
RESPONSIBILITY FOR EXECUTING POLICY:		ASSOCIATE VICE PRESIDENT FOR RESEARCH AND ECONOMIC DEVELOPMENT; IRB CHAIRPERSON, IRB VICE CHAIRPERSON, IRB MEMBERS					
LAST REVIEWED ON:		/ /		RESULTS:	REVISED		
APPROVAL AUTHORITY:		Associate Vice President for Research and Economic Development					
APPROVED BY:						DATE:	/ /

1. POLICY

Enrolling children into research studies presents especially difficult considerations for the IRB. Two factors make a case for research in children.

- Children differ markedly from both animals and adults, and therefore, these models cannot substitute as alternatives to testing in children.
- Lack of appropriate research in children will increase their risk of harm from exposure to practices and treatments untested in this population. In addition, new therapies could not be developed for diseases that specifically affect children.

However, research in children requires that the IRB carefully consider consent, beneficence, and justice. The determination of risk (possible harms) and possible benefit to the child is at the core of the concept of beneficence when considering research in a pediatric population. Therefore, the IRB must consider the degree of risk and discomfort involved in the research in relation to the direct benefits it offers to the child before it can determine whether or not the IRB has the authority to approve the study.

2. SPECIFIC POLICY

2.1 Definitions

The definitions in 45 CFR 46.102 are applicable to this subpart, in addition to the following definitions:

Assent: A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Benefit: A valued or desired outcome; an advantage.

Children:

DHHS: “children are 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.”(45 CFR 46.402(a)).

FDA: “children means persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law

of the jurisdiction in which the clinical investigation will be conducted.” (21 CFR 50.3(o))

- When research is conducted outside of North Dakota, the IRB consults legal counsel for assistance in applying applicable state and tribal laws to research involving human participants.

Dissent: An individual’s negative expressions, verbal and/or non-verbal, that they object to participation in the research or research activities.

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage, or procreation. North Dakota recognizes a minor as emancipated only upon marriage or having served in the armed forces.

Guardian:

DHHS: “guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.” (45 CFR 46.402(e))

FDA: “guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research.” (21 CFR 50.3(s))

- When research is conducted outside of North Dakota, the IRB consults legal counsel for assistance in applying applicable state and tribal laws to research involving human participants.

in loco parentis: Someone who acts in the place of a parent.

Legally Authorized Representative (LAR): 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 the procedure(s) involved in the research.

- When research is conducted outside of North Dakota, the IRB consults legal counsel for assistance in applying applicable state and tribal laws to research involving human participants.

Parent: A child's biological or adoptive parent.

Permission:

DHHS: "Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research" (45 CFR 46.402(c))

FDA: “Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be obtained in compliance with subpart B of this part and must include the elements of informed consent described in § 50.25.” (21 CFR 50.3(r))

Minimal Risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i)).

Minor: In North Dakota, minors are persons under eighteen years of age. Age must be calculated from the first minute of the day on which persons are born to the same minute of the corresponding day completing the period of minority.

Risk: The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study.

Secretary: The Secretary of the Department of Health and Human Services (DHHS) and any other officer or employee of the DHHS to whom authority has been delegated.

2.2 IRB Duties ([45 CFR 46.403](#))

Because of the vulnerability of children, special procedures are in place in the Federal Regulations that provide additional safeguards for the protection of children involved in research activities. The IRB will adhere to [45 CFR 46 Subpart D](#) or [21 CFR 50, Subpart D](#). The exemptions listed in [45 CFR 46.101\(b\)\(1\) through b\(6\)](#) are applicable for research involving children except for [45 CFR 46.101\(b\)\(2\)](#) for research involving surveys, interview procedures, or interventions with children.

2.2.1 Review of research involving children.

1. **Research not involving greater than minimal risk ([45 CFR 46.404](#)).** Research found by the IRB to present no greater than minimal risk to children may be conducted only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of at least one parent/guardian as set forth in [\(45 CFR 46.408\)](#). Such a finding must be documented.
2. **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects ([45 CFR 46.405](#)).** The IRB may approve research involving more than minimal risk to children but 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, only if the IRB finds and documents in the minutes of a convened meeting that:
 - The risk is justified by the anticipated benefit to the subjects
 - The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
 - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in [\(45 CFR 46.408\)](#).
3. **Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition ([45 CFR 46.406](#)).** The IRB may approve research involving greater than minimal risk to children 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, only if the IRB finds and documents in the minutes of a convened meeting that:
 - The risk represents a minor increase over minimal risk;
 - 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;
 - 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
 - Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in [\(45 CFR 46.408\)](#).

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](#)). HHS will conduct or fund research that the IRB does not believe meets the requirements of [§46.404](#), [§46.405](#), or [§46.406](#) only if:
- The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
 - The Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment has determined either:
 - (1) That the research in fact satisfies the conditions of [404](#), [405](#), or [406](#), or
 - (2) the following:
 - (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - (ii) The research will be conducted in accordance with sound ethical principles;
 - (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in [§46.408](#).

It is not anticipated that research in this category will be conducted at the University of North Dakota or other institutions governed by its IRB.

When reviewing research conducted on children, risk is defined in terms of minimal and greater than minimal risk, and may only be approved by the IRB as follows:

Risk determination	Benefit assessment	IRB’s action
Minimal	With or without direct benefit	Approvable
Greater than minimal risk*	Potential benefit to child	Approvable
Greater than minimal risk	No direct benefit to individual; offers general knowledge about the child’s condition or disorder	Approvable case-by-case*
Greater than minimal risk	No direct benefit to child; offers potential to, “understand, prevent, or alleviate a serious problem affecting the health and welfare of subjects”	Not approvable**
* Risk may not be more than a minor increase over minimal risk; consent of both parents required under normal circumstances. * Respect for persons requires oral communication with children younger than age 7 about the research and what they will experience to the extent of their development permits. **Approval to proceed with this category of research must be made by the Secretary of the HHS with input from selected experts, and following opportunity for public review and comment.		

2.2.2 Requirements for permission by parents or guardians and for assent by children ([45 CFR 46.408](#)).

1. In addition to the determinations required under other applicable sections of this subpart, the IRB shall 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. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children 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 children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. 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 in accord with [§46.116](#) of [Subpart A](#).
2. In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by [§46.116](#) of [Subpart A](#), that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under [§46.404](#) or [§46.405](#). Where research is covered by [§46.406](#) and [§46.407](#) and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
3. In addition to the provisions for waiver contained in [§46.116](#) of subpart A, 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 in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. 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.

If an Investigator is a mandated reporter and therefore required to report known or suspected child abuse, this must be disclosed and explained in the consent form.

4. Permission by parents or guardians shall be documented in accordance with and to the extent required by [§46.117](#) of [subpart A](#).
5. When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

2.2.3 Wards ([45 CFR 46.409](#))

1. Children who are wards of the state or any other agency, institution, or entity can be included in research approved under [§46.406](#) or [§46.407](#) only if such research is:
 - (1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

2. If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

3. RESPONSIBILITY

The IRB Coordinator is responsible for maintaining up-to-date review tools for review of research pertaining to vulnerable groups based on new and evolving applicable regulations and guidelines.

The IRB Chairperson and the IRB Coordinator are responsible for ensuring the IRB members are well versed in new and evolving regulations and guidelines pertaining to vulnerable populations.

The IRB Chairperson, IRB Coordinator, and/or IRB Secretary is responsible for selecting primary reviewers with appropriate expertise to conduct the reviews of such research, and for securing appropriate consulting expertise as needed for selected reviews.

The Primary Reviewer is responsible for conducting appropriate review of research planned for vulnerable populations, including an assessment of potential for coercion, in consultation with any appropriate experts and resources.

IRB Members are responsible for review of the research thoroughly enough to participate in the discussion at the convened IRB meeting.

4. APPLICABLE REGULATIONS AND GUIDELINES

The Belmont Report
 45 CFR 46: Subpart D
 45 CFR 46.122
 21 CFR 56.111
 OHRP IRB Guidebook

5. ATTACHMENTS

SC 503-A Checklist for Research Involving Children

6. PROCEDURES EMPLOYED TO IMPLEMENT THIS POLICY

Who	Task
<i>IRB Coordinator</i>	Maintain and update checklist to conform to applicable regulations and guidelines.
<i>IRB Chairperson, IRB Coordinator, IRB Secretary</i>	Select appropriate Primary Reviewers or obtain expert consultant.

<i>IRB Secretary</i>	Provide Primary Reviewers with appropriate checklist.
<i>Primary Reviewers</i>	Complete checklist during review of research and present recommendations at convened meeting. Confirm that proposal has informed consent and assent documents as appropriate.