



**DUKE UNIVERSITY HEALTH SYSTEM**  
**Human Research Protection Program**

**RESEARCH INVOLVING  
CHILDREN**

**11/20/2023**

**Note:** For exempt research involving children as subjects, see “Research for Which Review by the Duke University Health System Human Research Protection Program is Required”

**Note:** For research involving children who are wards of the State as participants, see “Research Involving Minors Who Are Wards of the State”

**I. OVERVIEW**

Children are a vulnerable research population and require additional protections when they are potential research subjects. HHS and FDA regulations require certain additional protections for children who are the subjects of research (45 CFR 46 Subpart D and 21 CFR 50 Subpart D). DUHS policy requires adherence to these regulations.

In addition, if research not regulated by the FDA involves:

- Pregnant minors, then the requirements of 45 CFR 46 Subpart B must also be met
- Incarcerated minors, then the requirements of 45 CFR 46 Subpart C must also be met.

Additional protections under HHS and FDA Subparts D include:

- Requiring IRB review of some research activities involving children that would otherwise be exempt if the research participants were adults instead
- Use of parental permission and child assent instead of the procedures for obtaining informed consent used for research involving adults
- Conditions for IRB approval of proposed research activities in four categories, depending on the level of risk and other features of the proposed research activity
- Review by the Secretary of the Department of Health and Human Services for research that an IRB finds not otherwise approvable
- Additional conditions for certain research activities involving children who are Wards of the State.

**II. DEFINITIONS**

The following terms, as defined by HHS and FDA Subparts D and other regulations, are important for understanding this policy.

1. **Assent** - a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
2. **Child/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.

North Carolina Law defines individuals less than 18 years of age to be minors, and children as defined in federal regulations, and Subpart D applies unless:

- The individual is married, OR
- The individual has been declared by a court order to be emancipated

If research is to be conducted outside of North Carolina, the investigator should check appropriate state laws and regulations to determine the definition of a child.

North Carolina law describes four medical conditions for which a minor may seek medical care for the prevention, diagnosis or treatment of the medical condition, and thus give informed consent for this medical care. These medical conditions are:

- Venereal disease and other reportable diseases
- Pregnancy
- Abuse of a controlled substance or alcohol
- Emotional disturbance

It is the policy of the DUHS IRB not to approve a child's involvement in research directed at any of these four medical conditions without the permission of the child's parents or guardian and the child's assent (when applicable).

3. **Guardian** - 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), 21 CFR 50.3(s)]. Under North Carolina law, a guardian of a child must be appointed by a court under Article 6 of Chapter 35A of the North Carolina General Statutes.
4. **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 examination or tests.
5. **Parent** - A child's biological or adoptive parent.
6. **Permission** - The agreement of parent(s) or guardian to the participation of their child or ward in research.
7. **Ward** - A "ward" or "Ward of the State" means a minor (typically under 18

years of age) who is under the legal custody of the State or any other agency, institution, or entity, in accordance with Federal, State, or local law. This may include, for example, a minor placed in foster care in accordance with applicable state law.

### **III. IRB JURISDICTION AND REVIEW**

The IRB must review research covered by Subpart D and approve only research that satisfies the conditions of all applicable sections of Subpart D.

The IRB must determine that whenever Subpart D applies, permission will be obtained from each child participant's parents or guardian, except as provided by the regulations, in addition to the child's assent when over 6 years of age (when applicable). These findings will be documented on a checklist and/or in the minutes for the meeting. Additionally, the IRB's determination of the need for one or two parents' signatures on the parental permission form will be documented in the minutes.

### **IV. RISK LEVEL AND PARENTAL PERMISSION REQUIREMENTS**

HHS regulations limit research involving children to those activities that meet one of four categories of research. These categories (specified in 45 CFR 46 Subpart D) are based on the level of risk and potential for benefit to the individual participant. Equivalent categories appear in the FDA regulations at 21 CFR 50 Subpart D, and are applied to all FDA-regulated clinical investigations that include children as participants.

The Federal regulations present specific requirements for obtaining permission from parents or legal guardians based on the level of risk and potential for benefit to the individual participant. The investigator must make adequate provisions for soliciting the permission of each child's parents or legal guardian as declared by the IRB (45 CFR 46.408(b), and 21 CFR 50.55(e) if applicable).

Permission by parents or guardians shall be documented in the same manner as required for other participants, unless permission by parents is waived (see below).

**A. Research not involving greater than minimal risk** (45 CFR 46.404 or 21 CFR 50.51) - To be approvable under this category, the IRB must find that:

1. No greater than minimal risk to children is presented, and
2. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth below.

Where parental permission is to be obtained, the IRB may find that the permission of **one parent** is sufficient for research in this category.

**B. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405 or 21 CFR 50.52)** – To be approvable under this category, the IRB must find that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being. The IRB must further find that:

1. The risk is justified by the anticipated benefit to the child,
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, and,
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth below.

Where parental permission is to be obtained, the IRB may find that the permission of **one parent** is sufficient for research in this category.

**C. 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 or 21 CFR 50.53)** - To be approvable under this category, the IRB must find 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. The IRB must further find that:

1. The risk represents a minor increase over minimal risk
2. Intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations
3. The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition, AND
4. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth below.

Research approved under this category requires that, when parental permission is to be obtained, **both parents** must give 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.

**D. 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 or 21 CFR 50.54) - If the IRB does not find that the research proposal meets any of the requirements set forth above, it may still approve the application but only if:

1. 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
2. The Secretary of the Department of Health and Human Services or the Commissioner of the FDA (as applicable), after consultation with a panel of experts in pertinent disciplines (for example, science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
  - a. That the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or §50.51, §50.52, or §50.53, as applicable, OR
  - b. The following are met:
    - 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, and
    - iii. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth below.

Research approved under this category requires that, when parental permission is to be obtained, **both parents** must give 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.

**V. ADDITIONAL FDA REGULATION OF PLACEBOS**

FDA does not consider the administration of a placebo to a child to offer a prospect of direct benefit to the recipient. (Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products – Federal Register 78(38):12937-12951). Consequently, for a study of a drug or biologic (whether investigational or FDA-approved) versus a placebo, with no other therapy permitted (standard of care and/or known effective treatment is withheld), the placebo recipient would be viewed as having no prospect of direct benefit from participating in the study.

In such a circumstance, the risks in the placebo control group should present no more than minimal risk or a minor increase over minimal risk. The placebo control arm of such a study must be approvable under either 21 CFR 50.51 or

21 CFR 50.53, or the clinical investigation must be referred for review under 21 CFR 50.54. Those in the arm that receive the investigational product often would be viewed as having the prospect of direct benefit, and that portion of the study could be approvable under 21 CFR 50.52. **Each study arm requires a separate risk determination.**

However, in a study where one study drug or study biologic is given in addition to standard therapy specified by the protocol (with drugs and doses delineated) compared with a placebo given in addition to standard therapy specified by the protocol (with drugs and doses delineated), the placebo recipient would be viewed as having the prospect of direct benefit from the standard therapy, and the study would be approvable under 21 CFR 50.52. Also those in the arm that receive the investigational product and the standard therapy would be viewed as having the prospect of direct benefit, and that portion of the study could also be approvable under 21 CFR 50.52.

With respect to the criteria that must be met for approval under 21 CFR 50.53, the inclusion of children without the disorder or condition under study would not meet the requirement of 21 CFR 50.53(c) that “the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition.”

## **VI. WAIVER OF PARENTAL OR LEGAL GUARDIAN PERMISSION**

In addition to the provisions for waivers contained in 45 CFR 46.116, if the IRB determines that the research protocol is designed to study conditions or participants for which parent or legal guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), the IRB may waive the consent requirements if both of the following conditions are met:

1. An appropriate mechanism for protecting the children who will participate as participants in the research is substituted, and
2. The waiver is consistent with Federal, State, or local law.

The choice of an appropriate mechanism (for example, appointing a child advocate or an assent monitor) for protecting children participating in research depends upon the nature and purpose of the activities described in the research plan, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition.

The requirement for parental or guardian permission also may be waived under the circumstances in which consent may be waived under 45 CFR 46.116.

Note that for FDA regulated research, no such waiver of parental permission is permitted.

## **VII. REQUIREMENTS AND DOCUMENTATION OF ASSENT OF CHILDREN**

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

The investigator must make adequate provisions for soliciting the assent of a child participant when the children are capable of providing assent. In determining whether children are capable of assenting, the investigator should 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 research protocol, or for each child. Unless otherwise specified by the investigator and approved by the IRB, the investigator will solicit the assent of children 6 years of age or older. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition.

When the IRB determines that assent of a child is required, it shall also determine whether documentation is required.

## **VIII. WAIVER OF ASSENT**

The assent of children is not a necessary condition for proceeding with the research if the IRB determines that either of the following is true:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted, OR
- 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.

If some of the children age 6 years and above would not be able to provide meaningful assent, the investigator will indicate how they will be identified. The IRB will determine and document whether their selection is justified.

The requirement for assent of the child participant also may be waived under the circumstances in which consent may be waived under 45 CFR 46.116.

For FDA regulated research, the requirement for assent of the child participant may be waived according to 21 CFR 50.55(d).

## **IX. DISSENT**

The IRB may request that the investigator include a description of behaviors that will be viewed as indicators that the child does not wish to participate in the research (such as crying, moving away from the investigator, or being unwilling to complete tasks). Therefore, the investigator may not rely solely on the absence of verbalized objection as the basis for deciding that assent has been given.

When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that a child's dissent, which should normally be respected, may be overruled by the child's parents or legal guardian.

Finally, even where the IRB determines that the children are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults.

#### **X. CHILDREN IN RESEARCH WHO TURN EIGHTEEN**

When a child who was enrolled in research with parental or guardian permission subsequently reaches age 18 years, the legal age of consent to the procedures involved in ongoing research, the individual's participation in the research is no longer regulated by the requirements of this policy or by 45 CFR 46.408 or 21 CFR 50.55 regarding parental or guardian permission and subject assent.

Unless the IRB determines that the requirements for obtaining informed consent can be waived, the investigator is expected to seek and obtain the legally effective informed consent, as described in 45 CFR 46.116 and 21 CFR 50.20 and .25, for the now-adult participant for any ongoing interactions or interventions with the participants. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(f), or in accordance with FDA guidance on waivers, and the IRB finds and documents that the required conditions are met.

Similarly, if the research does not involve ongoing interactions or interventions with the participants, but continues to meet the regulatory definition of "human subjects research" (for example, it involves the continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator), then it would be necessary for the investigator to seek and obtain the legally effective informed consent of the now-adult participants. The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(f) of the requirements for obtaining informed consent in order for the individuals to continue their participation in the research.

#### **XI. DOCUMENTATION**

Permission by parents or guardians shall be documented in the same manner as required for other participants. When the IRB determines that assent of a child is required, it shall also determine whether documentation is required.

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