

NIH HRPP SOP 14D v1

**HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL &  
IMPLEMENTATION**

**OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS**

**SOP Number: SOP 14D**

**SOP Title: RESEARCH INVOLVING CHILDREN**

**Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB  
Chairs, IRB Administrators, Protocol Navigators**

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## **SOP 14D RESEARCH INVOLVING CHILDREN**

### **14D.1 PURPOSE**

This SOP discusses the requirements for NIH investigators, IRBs and others when conducting and reviewing research involving children.

### **14D.2 POLICY**

- A. The NIH HRPP follows the requirements of this SOP which are consistent with Federal Regulations for the Protection of Human Subjects (45 CFR 46) Subpart D “Additional Protections for Children Involved as Subjects in Research” (See Appendix A-Links to web sites). For the applicable requirements of the Food and Drug Administration (FDA), see 21 CFR 50, Subpart D – Additional Safeguards for Children in Clinical Investigations (See Appendix A-Links to web sites). The requirements of this SOP are in addition to those imposed under other subparts of 45 CFR 46 and other relevant SOPs.
- B. Children must be included in research unless there are scientific justifications not to include them (see 14D.5.1.B, below).
- C. There are exemptions that may not apply to research involving children. The exemption for research involving the use of educational tests (45 CFR 46.101(b)(2)) is narrowed in scope when applied to involving children (for more information, see SOP 6 “Determinations, Including Exemptions, Made by the Office of Human Subjects Research Protections (OHSRP) Under 45 CFR 46”). The other five exemptions found at 46.101(b) apply to research involving children in the same way that they apply to research involving adults.

- D. The Secretarial waiver of informed consent in certain emergency research may be applicable to research involving children (see SOP 12 “Requirements of Informed Consent”).

### 14D.3 DEFINITIONS

- A. **Advocate** is 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 investigators(s), or the guardian organization.
- B. **Assent** means a child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent (45 CFR 46.402(b)).
- C. **Benefit** is a valued or desired outcome of the research for the child subjects.
- D. **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)).
- E. **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)).
- F. **Minimal Risk** means that 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 (see 45 CFR Part 46 102(i)).

- G. **Parent** means a child's biological or adoptive parent (45 CFR 46.402(d)).
- H. **Permission** means the agreement of parent(s) or guardians(s) to the participation of their child or ward in research. (45 CFR 46.402(c)).
- I. **Risk** is the probability of harm (physical, emotional, social, or economic). The probability of harm may vary from minimal to substantial.
- J. **Secretary** means the Secretary of Health and Human Services and any other officer or employee of DHHS to whom authority has been delegated.
- K. **Ward** means a child who is placed under the protection of and in the legal custody of the State or other agency, institution, or entity (including guardians), consistent with applicable State or local law.

#### **14D.4 RESPONSIBILITIES OF PRINCIPAL INVESTIGATORS WHEN APPLYING FOR INITIAL IRB REVIEW FOR RESEARCH INVOLVING CHILDREN**

When conducting research protocols involving children, PIs shall provide information to the IRB required by this and other HRPP SOPs and the NIH Intramural Clinical Initial Protocol Application, including the Application's Supplement D (Research Involving Children).

#### **14D.5 RESPONSIBILITIES OF NIH IRBS REGARDING REVIEW OF RESEARCH INVOLVING CHILDREN**

### **14D.5.1 APPROVAL OF RESEARCH INVOLVING CHILDREN**

An IRB may approve research involving children only if it has determined and documented in its minutes that:

- A. The research is scientifically sound and significant.
- B. In keeping with ethical guidelines on research involving children, when appropriate, earlier studies have been conducted first on animals and adult humans, and then on older children before involving younger children and infants. Investigators must provide and IRBs are responsible for approving ethical and scientific justifications for recruiting children within the age range stipulated in the protocol.
- C. Risks to children are minimized using the safest procedures available consistent with sound research design and, whenever feasible, using procedures performed for diagnostic or treatment purposes.
- D. Adequate provisions are made to protect the privacy of children and their parents or guardians, and to maintain the confidentiality of data.
- E. Subjects will be selected in an equitable manner; and
- F. The conditions of all other applicable sections of this SOP are met.

### **14D.5.2 ALLOWABLE CATEGORIES OF RESEARCH**

- A. The HHS federal regulations permit four categories of research involving children:
  - 1. Category 1. 45 CFR 46.404, Research not involving greater than minimal risk

2. Category 2. 45 CFR 46.405, Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
  3. Category 3. 45 CFR 46.406, 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
  4. Category 4. 45 CFR 46.407, Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
- B. Each category imposes special requirements upon the IRB's reviews of any study involving children. The IRB is responsible for determining into which of the four categories of research the study belongs and documenting in the minutes and IRB records its rationale for this choice. The IRB should consult the PI in making this determination.
- C. In the case of Category 4 (45 CFR 46.407), which requires a determination by the Secretary, DHHS, the IRB will forward the approved research protocol to the Director, Office of Human Subjects Research Protections (OHSRP) who will present it to the Deputy Director of Intramural Research (DDIR) (the Institutional Official) or designee for approval. Upon approval by the DDIR, OHSRP will forward the protocol to the Office for Human Research Protections (OHRP) for review by the Secretary, DHHS and, if appropriate, the Commissioner, FDA per 21 CFR 50.54.
- D. For FDA requirements regarding research in children see 21 CFR 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (See Appendix A- Links to web sites).

## **14D.6 RESPONSIBILITIES OF NIH PIS AND IRBS REGARDING REQUIREMENTS FOR OBTAINING AND DOCUMENTING PERMISSION BY PARENTS OR GUARDIANS**

### **14D.6.1 OBTAINING OR WAIVING PARENTAL PERMISSION**

In addition to the other applicable sections of Subpart D, the IRB must determine, in accordance with and to the extent that is required by 46.116, as described in SOP 12 (“Requirements of Informed Consent”), that adequate provisions have been made for soliciting the permission of each child’s parent or guardian. This and additional requirements for obtaining permission are described in 45 CFR 46.408(b). When parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research conducted under regarding categories 1 and 2 (see above 14D.5.2) and the IRB should document this finding. IRBs should also document if consent from both parents is required. Where research is conducted under categories 3 and 4 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. If an IRB chooses to waive the consent requirements of Subpart A and 46.408(b), the requirements of 45 CFR 46.408(c) must be followed.

### **14D.6.2 DOCUMENTATION OF PARENTAL PERMISSION**

Permission from parents or legal guardians must be documented in accordance with and to the extent required by 46.117 (see SOP 12 “Requirements of Informed Consent”), including possible waiver of documentation of informed consent (46.408(d)).

## **14D.7 RESPONSIBILITIES OF NIH PIS AND IRBS REGARDING REQUIREMENTS FOR OBTAINING AND DOCUMENTING ASSENT BY CHILDREN**

### **14D.7.1 PI RESPONSIBILITIES**

- A. Every protocol involving children shall include a discussion of how assent will be obtained, if at all, for that particular study. This may take the form of a description of how information will be verbally communicated to the child or a sample written assent document appropriate to the age and comprehension level of the children to be enrolled. A written assent should be obtained when the IRB determines it to be a meaningful process within the context of the particular research study. For subjects at the NIH Clinical Center, NIH form 2514-2 (Attachment A) is used.
- B. If obtaining assent is not anticipated in the protocol, the PI is obligated to justify to the IRB why assent (written or oral) is not possible.

### **14D.7.2 IRB RESPONSIBILITIES**

- A. The IRB shall determine that adequate provisions are made for:
  - 1. Soliciting the assent of the children when in the determination of the IRB they are capable of assent, see **14D.7.2.B**, below, and Appendix B (Guidelines on Children's Assent). This appendix is based on the NIH Medical Administrative Series 92-5 "Research Involving Children and Children's Assent." (See Appendix A- Links to Web sites.)
  - 2. Considering the objections to participation by a child who is capable of assent. A child's objections(s) should be binding unless the research holds out a prospect of direct benefit that is important to the health and well being of the child and that is available only in the context of research.
  - 3. Monitoring the solicitation of assent when appropriate.

- B. 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 study, or for each child, as the IRB deems appropriate.
  - 1. The assent of child research subjects is not a necessary condition for proceeding with the research in the infrequent circumstances in which the IRB determines that (i) some of all of the children's capabilities are so limited that they cannot reasonably be consulted, or (ii) 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.
  - 2. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement in circumstances in which consent may be waived in accord with 45 CFR 46.116 (found in the provisions in SOP 12 "Requirements of Informed Consent"). (45 CFR 46.408(a)).

### **14D.7.3 DOCUMENTATION OF ASSENT**

If an IRB determines that assent will be obtained, it shall determine whether, and how, it shall be documented (46 CFR 46.408(e)).

- A. If assent is obtained verbally, this should be documented on the research consent form signed by the parents/guardians.
- B. When a written assent document is used, the signatures of the child and investigator should be documented on the assent form. The signatures of the parent(s)/guardian(s), investigator and a witness (when applicable) will be documented on the consent form (for more information see SOP 12, "Requirements for Informed Consent").

#### **14D.7.4 RECONSENT OF MINORS WHO REACH AGE OF CONSENT WHILE ON A RESEARCH STUDY**

- A. Unless the IRB determines that the requirements for obtaining informed consent can be waived, the PI should seek and obtain the legally effective informed consent of the now-adult subject.
  
- B. The PI should seek and obtain the legally effective informed consent of the now-adult subject even if the research does not involve any ongoing interactions or interventions with the subject, but continues to meet the regulatory definition of “human subjects research” ( e.g., it involves the continued analysis of identifiable specimens or data). In these circumstances, if appropriate, the IRB may consider a waiver under 45 CFR 46.116 (d).

#### **14D.8 CHILDREN WHO ARE WARDS**

- A. Children who are wards of the State or any other agency, institution, or entity can be included in approved Category 3 (45 CFR 46.406) or Category 4 (45 CFR 46.407) research 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.
  
- B. If the research meets the condition(s) above in paragraph A, the IRB must 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 must 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. (45 CFR 46.409).

## **LIST OF APPENDICES**

Appendix A- Links to web sites

Appendix B- Guidelines on Children's Assent

## **LIST OF ATTACHMENTS**

Attachment A: NIH Form 2514-2

## APPENDIX A - LINKS TO WEB SITES

- A. 45 CFR 46 Subpart D “Additional Protections for Children Involved as Subjects in Research”:  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
  
- B. 21 CFR 50, Subpart D – Additional Safeguards for Children in Clinical Investigations
  
- C. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.4>
  
- D. NIH Medical Administrative Series 92-5 “Research Involving Children and Children’s Assent.”
  
- E. <http://cc-internal.cc.nih.gov/policies/PDF/M92-5.pdf>
  
- F. OHSR Special Protections for Children as Research Subjects.  
<http://www.hhs.gov/ohrp/policy/populations/children.html>
  
- G. OHSR Children Involved as Subjects in Research: Guidance on the HHS 45.CFR.46.407 (“407”) Review Process.  
[http://www.hhs.gov/ohrp/policy/populations/guidance\\_407process.html](http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html)
  
- H. OHSR Research with Children FAQs.  
<http://answers.hhs.gov/ohrp/categories/1570>

## **APPENDIX B: GUIDELINES ON CHILDREN'S ASSENT**

**(This is adapted from MAS 92-5 – “Research Involving Children and Children’s Assent to Research”)**

The following guidelines are intended to assist the investigator and the IRB to formulate assent procedures that will best serve the needs of the children who participate in a protocol.

A. Critical to the assent process is consideration of the maturation level of the children’s thought processes and capacities for comprehension:

1. A child with normal cognitive development becomes capable of meaningful assent at about the age of 7 years, although there is a wide range of variation.
2. Time is not similarly comprehended at all ages. A discussion of time requirements in a research protocol must be appropriate to the child's level of understanding.
3. Age is only a gross index of mental level and reasoning capacity.
4. A child's level of comprehension and reasoning will be altered by states of anxiety, and physical and emotional disturbances.

B. The protocol should be explained in such a manner that the child can provide a meaningful and informed assent. This explanation should include:

1. A reason for the child being at the research facility; i.e., relate the child's presence at the hospital to something meaningful in his/her experience.
2. Realistic expectations concerning what a child will experience in the hospital, including:
  - a. staying in bed....or not

- b. going home....or staying in the hospital
  - c. separation from the parents/friends .... or not
  - d. supervision by doctors and nurses
  - e. presence of other patients.
3. A description of specific procedures and the immediate consequences of those procedures, e.g., pain, falling asleep, medication by a tube put into the arm, how the child will look different or how his/her body might be changed as result of participation in the study, etc.
4. An explanation of the reason for a study and the hoped for benefits to the child, or how the study accomplishes benefits for other children.
- C. Children involved research which holds no anticipated benefit to them as individuals may withdraw or choose not to participate in the study at all. Since children (to age 7, for example) may not be accustomed to this type of control over what they are permitted to do, this right to dissent, if granted, may be misinterpreted. It is the investigator's responsibility to guide both the child and parents/guardians in this decision.