HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL & IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 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

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SOP 14D - RESEARCH INVOLVING CHILDREN

INTRODUCTION

This Standard Operating Procedure (SOP) highlights the most common issues that arise at NIH with regard to research with children, but the SOP is not a complete set of regulatory requirements. Therefore, please refer to 45 CFR 46, Subpart D, attached as **Appendix A**, which is hereby incorporated into this SOP.

14D.1 PURPOSE

This SOP discusses the requirements for NIH investigators, Institutional Review Boards (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 (see **Appendix A**). 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 **References**). 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 and/or ethical reasons 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 - Processes for Determinations Made by the Office of Human Subjects Research Protections (OHSRP)). 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 for 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 the US Department of Health and Human Services (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 OF RESEARCH INVOLVING CHILDREN

When conducting research protocols involving children, Principal Investigators (PIs) shall provide information to the IRB required by applicable HRPP SOPs and the NIH Intramural Clinical Initial Protocol Application, including information that is described in Supplement H, Guidance Regarding Research Involving Children (**Appendix B)**.

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 DHHS 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 review of any study involving children. The IRB is responsible for determining into which of the four categories of permitted research the study belongs and it must document its rationale for this decision in the minutes and IRB records. The IRB should consult the PI in making this determination.

C. In the case of Category 4 (45 CFR 46.407), a determination by the Secretary, DHHS is required. 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 **References**).

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

When reviewing research involving children, the IRB must ensure, that adequate provisions have been made for soliciting the permission of each child's parent or guardian in accordance with, and to the extent that is required, by 45 CFR 46.116, and as described in SOP 12 - Requirements for Informed Consent. 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 categories 1 and 2 (see **14D.5.2** above) and the IRB should document this finding. IRBs should also document if permission 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.

In cases where parents share joint legal custody for medical decision-making of a child (e.g., by a custody agreement or court order), both parents must give their permission regardless of the risk level of the research. Exceptions may include if one parent has since died, become incompetent, or is not reasonably

available (e.g., in prison). Guidance from the Office of the General Counsel should be sought if you have questions about the legal custody of a child or the availability of a parent.

If an IRB chooses to waive the consent requirements of Subpart A and 45 CFR 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 45 CFR 46.117 (see SOP 12 - Requirements for Informed Consent), including possible waiver of documentation of informed consent (45 CFR 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 further guidance see **Appendix C**.

B. If obtaining assent is not anticipated in the protocol, the PI must explain 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 children when the IRB determines that children are capable of assent, see **14D.7.2.B**, below, and **Appendix C**. This appendix is based on the Medical Administrative Series 92-5

"Research Involving Children and Children's Assent in Research" (see **References**). And ensuring that children have not withdrawn assent.

2. A child's failure to assent should be binding unless the research holds out a prospect of direct benefit that is important to the health and wellbeing of the child and that is available only in the context of research and the IRB has determined, consistent with regulations, that assent is not required.

3. Monitoring the solicitation of assent when appropriate.

4. Re-consenting minors when they reach the age of consent, if applicable. See **14D.8** for guidance.

B. The IRB will determine and document whether assent is a requirement of all, some, or none of the children on a protocol. When assent is not a requirement for some children, the IRB will document which children are not required to assent.

C. 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 circumstances in which the IRB determines that (i) some or 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 accordance with 45 CFR 46.116 and 45 CFR 46.408(a) (see SOP 12 - Requirements for Informed Consent for additional guidance).

14D.7.3 DOCUMENTATION OF ASSENT

A. If an IRB determines that assent will be obtained, it shall determine whether, and how, it shall be documented (46 CFR 46.408(e)). 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 (see SOP 12 - Requirements for Informed Consent).

14D.8 RESPONSIBILITIES OF NIH PIS AND IRBS REGARDING CONSENTING MINORS WHO REACH THE AGE OF CONSENT WHILE ON A RESEARCH STUDY, INCLUDING THOSE WHO ARE OR MAY BE UNABLE TO CONSENT

A. PIs should obtain consent from minors previously enrolled on protocols once the minors reach the age of consent[1] pursuant to the procedures outlined in SOP 12 – Requirements for Informed Consent. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject.

B. The PI should seek and obtain the legally effective informed consent of the now-adult subject unless the IRB has determined and documented that the requirements for obtaining informed consent can be waived under 45 CFR 46.116 (d).

C. 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

[1] For the purpose of consent at the NIH Clinical Center (CC), an adult is anyone 18 years or older or an emancipated minor (such as a minor who is married or a parent). At non-CC NIH sites applicable local, state or foreign law is followed in the absence of applicable U.S. Federal law.

circumstances, if appropriate, the IRB may consider a waiver under 45 CFR 46.116 (d).

D. If applicable, PIs should outline in their protocols how consent will be obtained when minor subjects reach the age of consent to ensure a smooth transition for subjects and their families. IRBs should review these provisions to ensure that they are adequate. Consideration should be given to forewarning subjects and their families at the time of enrollment that there will be a need to consent the minor subject on reaching the age of consent. This information can prevent a situation where parents might feel that the act of consenting is questioning a prior decision to enroll their child in a study.

E. In instances where an older minor subject might be cognitively impaired and is likely to be unable to provide consent as an adult, an advanced discussion of this possibility may help prepare parent(s)/ guardian(s) for next steps (e.g., whether they can act as a legally authorized representative in the context of NIH intramural research when the minor becomes an adult) (see SOP 14E - Research Involving Adults Who Are or May Be Unable to Consent).

F. For now-adult subjects who are unable to provide on-going consent, the PI should follow the guidance outlined in SOP 14E - Research Involving Adults Who Are or May Be Unable to Consent, unless the IRB has waived the requirement for informed consent.

14D.9 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 above condition(s), the IRB must require the 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 an 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. Additionally, the advocate must not be associated in any way (except in the role as an advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. (45 CFR 46.409).

REFERENCES

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: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.20.4

C. Medical Administrative Series 92-5 “Research Involving Children and Children’s Assent to Research”: http://cc-internal.cc.nih.gov/policies/PDF/M92-5.pdf

D. OHRP “Special Protections for Children as Research Subjects”: http://www.hhs.gov/ohrp/policy/populations/children.html

E. OHRP “Children as Research Subjects and the HHS “407” Process”: http://www.hhs.gov/ohrp/policy/populations/guidance_407process.html

F. OHRP “Research with Children FAQs”: http://www.hhs.gov/ohrp/policy/faq/children-research/index.html

LIST OF APPENDICES

APPENDIX A - 45 CFR 46 SUBPART D – ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED AS SUBJECTS IN RESEARCH

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at§46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at§46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of subpart A are applicable to this subpart.

[48 FR 9818, Mar.8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991.]

§46.402 Definitions.

The definitions in §46.102 of subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *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.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) *Parent* means a child's biological or adoptive parent.

(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.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds 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, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) 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

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§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.

HHS will conduct or fund research in which the IRB finds 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, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) 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;

(c) 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

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§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.

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:

(a) 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

(b) the Secretary, 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:

(1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, 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.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) 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.

(b) 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.

(c) 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.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by§46.117 of subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) 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.

(b) 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.

APPENDIX B - SUPPLEMENT H – GUIDANCE REGARDING RESEARCH INVOLVING CHILDREN AS SUBJECTS

Children as Subjects (*check all that apply)*

Where will the children participate?

__ NIH Clinical Center
__ Other NIH Site Specify:
__ Home
__ School
__ Outside Clinical Site
__ Other, specify:

If yes, have you obtained the necessary permission from the school district?
__ Yes __ No *(Attach documentation of permission)*

Are any of the children wards of a State or any other agency, institution, or entity? (see 45 Part 46.409) __ Yes __ No

Risk/Benefit Assessment and parental permission for participation

Check the boxes below that best represents the degree of risk and benefit to which the children in this study will be exposed based on 45 CFR 46 Subpart D and, if applicable, 21 CFR 50 Subpart D.

Note: more than one category may be indicated such as when a protocol involves both a study group and a control group; in these cases, please specify the cohort.

For each risk category, please select the appropriate permission level.

In general, permission from both parents is required for research involving children 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. For Categories 1& 2, the IRB may find that the permission of one parent is sufficient for compliance with 45 CFR 46 but NIH may require permission of both parents.

Waiver of parental permission for research not regulated by the FDA: The IRB may waive the requirement for obtaining consent from a parent or legal guardian, except when research is regulated by the FDA (21 CFR 50.55), if:

The research meets the provisions for waiver in SOP 12-Requirements for Informed Consent, or

The IRB determines that the research study is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), provided an appropriate mechanism for protecting the children participants is substituted, and that the waiver is not inconsistent with applicable 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.

__ The proposed research poses risk no greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., minimal risk) (45 CFR 46.404).

__ Permission will be obtained from both parents 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.

__ Permission from only one parent is being requested

__ A waiver of parental permission is being requested *(Complete Supplement L and provide justification for a waiver in the protocol.)*

__ The proposed research poses a greater than minimal risk with the potential for direct benefit to subjects (45 CFR 46.405).

Address in the protocol, how the benefit to risk assessment is at least as favorable as that presented by alternative approaches.

__ Permission will be obtained from both parents 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.

__ Permission from only one parent is being requested

__ A waiver of parental permission is being requested *(Complete Supplement L and provide justification for a waiver in the protocol.)*

__ The proposed research poses a greater than minimal risk with no potential for direct benefit to the individual subjects, but is likely to yield generalizable knowledge about the subjects' conditions (45 CFR 46.406).

Please address the following in the protocol:

- How the risk of the protocol presents a minor increase over minimal risk.
- How the procedure(s) present experiences to subjects that are reasonably commensurate with those inherent in their actual or expected situations.
- How the knowledge to be gained is of vital importance for the understanding or amelioration of the condition.

__ Permission will be obtained from both parents 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.

__ The proposed research does not meet the criteria in the above categories but presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children (45 CFR 46.407).

(Requires approval by Deputy Director for Intramural Research and the Secretary of Health and Human Services and/or the Commissioner of Food and Drugs, as applicable.)

Address the benefit to risk ratio in the protocol and discuss the ways in which the study presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.

__ Permission will be obtained from both parents 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.

Parental Permission in a Group Setting

What permission will be obtained from the parents if the research is being conducted in a group setting (e.g., a classroom)? (Explain in the protocol what provisions have been made for children whose parents have not given permission for them to participate.)

Assent from Children

Adequate provisions must be made for soliciting the assent of children when in the judgment of the IRB the children are capable of providing assent and for soliciting the permission of their parents or guardians.

Please indicate below whether the children you will study are generally capable of providing assent; evaluate age, maturity and psychological state of the children involved.

__ All are capable
__ None are capable (Explain in the protocol)
__ Some are capable (Explain in the protocol)

Describe in the protocol how assent will be obtained, including what information will be provided to the subjects

APPENDIX C - 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.

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

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.

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.

Age is only a gross index of mental level and reasoning capacity.

A child's level of comprehension and reasoning will be altered by states of anxiety, and physical and emotional disturbances.

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

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.

Realistic expectations concerning what a child will experience in the hospital, including, for example:

staying in bed....or not

going home....or staying in the hospital

separation from the parents/friends .... or not

supervision by doctors and nurses

presence of other patients.

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 a result of participation in the study, etc.

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.