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1. SCOPE

Pursuant to 45 CFR 46, Subpart D (Additional Protections for Children Involved as Subjects in Research), the Purdue University Institutional Review Board (IRB) must review all non-exempt research involving children and may approve only research which satisfies the conditions listed in this policy.

The procedures below apply to Investigator requests to conduct non-exempt research that involves children as research subjects. The following definitions and procedures apply to research conducted within the state of Indiana. Other laws may apply if an Investigator conducts research involving children outside the state of Indiana.

2. DEFINITIONS

2.1 *Assent.* An individual's affirmative agreement to participate in research obtained in conjunction with permission of the individual's parents or legally authorized representative. Mere failure to object should not, absent affirmative agreement, be construed as assent.

2.2 *Benefit.* A valued or desired outcome; an advantage.

2.3 *Children.* According to the federal regulations, 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. Per Indiana State Law, "minors" (that is, persons less than 18 years of age) are considered "children" for purposes of this policy.

EXCEPTION: Per Indiana Code 16-36-1-3, a minor may consent for medical treatment on his/her behalf if certain conditions are met. Accordingly, it is the position of the Human Research Protection Program (HRPP) that a minor may consent to participate in research, if any of the following are true:

2.3.1 The minor is emancipated;

2.3.2 The minor is at least fourteen (14) years of age, not dependent on a parent for support, is living apart from parents or from an individual *in loco parentis*; and is managing the minor's own affairs;

2.3.3 The minor is or has been married;

2.3.4 The minor is in the military service of the United States; or

2.3.5 The minor is authorized to consent to their health care by any other statute.

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

- 2.5** *Greater Than Minimal Risk.* The probability and magnitude of harm or discomfort anticipated in the research are greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- 2.6** *Guardian.* An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. The FDA includes in its definition that this individual can also consent on behalf of a child to participate in research.
- 2.7** *In loco parentis.* Someone who acts in the place of a parent.
- 2.8** *Legally Authorized Representative (LAR).* Defined in the federal regulations as an individual or a 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. In Indiana, a health care representative (appointed in accordance with Indiana Code 16-36-1-7) is the equivalent of the federally defined LAR.
- 2.9** *Minimal Risk.* Level of risk in which 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 of a normal healthy person living in a safe environment or during the performance of routine physical or psychological examinations or tests.
- 2.10** *Parent.* A child's biological or adoptive parent.
- 2.11** *Permission.* The agreement of parent(s) or guardian(s) to the participation of their child or ward in research.
- 2.12** *Persons authorized to consent for incapable parties (children).* Per Indiana Code 16-36-1-5, consent to health care for a minor not authorized to consent may be given by any of the following:
- 2.12.1 A judicially appointed guardian of the person or a representative appointed.
- 2.12.2 A parent or an individual *in loco parentis* if:
- 2.12.2.1 There is no guardian or other representative described in 2.12.1 above;
- 2.12.2.2 The guardian or other representative is not reasonably available or declines to act; or
- 2.12.2.3 The existence of the guardian or other representative is

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unknown to the health care provider.

2.12.3 An adult sibling of the minor if:

- 2.12.3.1 There is no guardian or other representative described in 2.12.1 above.
- 2.12.3.2 A parent or an individual *in loco parentis* is not reasonably available or declines to act; or
- 2.12.3.3 The existence of the parent or individual *in loco parentis* is unknown to the health care provider after reasonable efforts are made by the health care provider to determine whether the minor has a parent or an individual *in loco parentis* who is able to consent to the treatment of the minor.

2.12.4 A grandparent of the minor if:

- 2.12.4.1 there is no guardian or other representative described in 2.12.1 above;
- 2.12.4.2 a parent, an individual *in loco parentis*, or an adult sibling is not reasonably available or declines to act; or
- 2.12.4.3 the existence of the parent, individual *in loco parentis*, or adult sibling is unknown to the health care provider after reasonable efforts are made by the health care provider to determine whether the minor has a parent, an individual *in loco parentis*, or an adult sibling who is able to consent to the treatment of the minor.

2.12.5 An individual delegated authority to consent has the same authority and responsibility as the individual delegating the authority.

2.12.6 An individual authorized to consent shall act in good faith and in the best interest of the individual incapable of consenting.

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

2.14 *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.

3. PROCEDURES

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3.1 IRB Review and Approval – General Requirements

3.1.1 The IRB must apply special considerations to all reviewed research in which children are the target population or may constitute some of the subject population. When the IRB reviews research involving children as subjects it must consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the child-subject or to society as a whole. In calculating the degree of risk and benefit, the IRB should weigh the circumstances of the subjects under study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

3.1.1.1 Procedures that usually present no more than minimal risk to a healthy child include urinalyses, obtaining small blood samples, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. However assessing the probability and magnitude of risk in sick children may be different and varied depending on the diseases or conditions the subjects may have.

3.1.1.2 Although assessing the limits of minimal risk needs to be done on a case-by-case basis, the IRB should consider biopsy of internal organs, spinal taps, or use of drugs whose risks to children have not yet been established as among the riskier procedures (greater than minimal risk).

3.1.1.3 In assessing the possible benefits of research participation for children, the IRB should consider the variability in health statuses among potential subjects (e.g., normal, healthy child vs. a child suffering from a disease or significant medical condition). Therefore, the IRB should consider the health status of a child and the likelihood of progression to a worsened state without research intervention.

3.1.2 The IRB must classify research involving children into one of four categories and document its discussion of the risks and benefits of the research study in order to approve such research. The four categories of research involving children that may be approved are based on degree of risks and benefit to the individual subjects. These categories are:

3.1.2.1 **Research not involving greater than minimal risk to children (45 CFR 46.404)**

When the IRB determines that no greater than minimal risk to children is presented, the IRB may approve the research only if

the IRB finds that adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians.

3.1.2.2 **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child (45 CFR 46.405)**

When the IRB determines 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 child, or by a monitoring procedure that is likely to contribute to the child's well-being, the IRB may approve the research if it finds that

- (a) the risk is justified by the anticipated benefit to the children;
- (b) the relation of the anticipated benefit to the risk is at least as favorable to the children 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 legal guardians.

3.1.2.3 **Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition (45 CFR 46.406)**

When the IRB determines 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 child but is likely to yield generalizable knowledge about the child's disorder or condition, the IRB may approve the research if it 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 improvement of the subjects' disorder or condition; and

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(d) adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians.

3.1.2.4 **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)**

When the IRB determines that the research does not meet the requirements in any of the above three categories, the IRB may only approve the research if it 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. Additionally, if the research is conducted or supported by the DHHS, the Secretary (through the Office for Human Research Protections (OHRP)) after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law and following opportunity for public review and comment, must determine that the research either:

(a) does in fact satisfy the conditions of 45 CFR 46.404, 45 CFR 46.405, 45 CFR 46.406; or

(b) presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, will be conducted with sound ethical principles and finds adequate provisions have been made for soliciting the assent of children and the permission of their parents or legal guardians.

Important Note: Research that is conducted or supported by DHHS that the IRB determined met 45 CFR 46.407 cannot be finally approved until a determination by the Secretary of DHHS (through OHRP) is received.

3.2 Adequate Provisions for Assent of Children

3.2.1 In accordance with 45 CFR 46.408(a) and 21 CFR 50.55(a), the IRB must determine that adequate provisions are made for soliciting the assent of children, when in the judgment of the IRB the children are capable of providing assent. Assent is typically required for children ages seven and older, but may be appropriate for younger children depending on their aptitude/ability.

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- 3.2.2 In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved in a particular research study, or for each child, as the IRB deems appropriate. The child should be given an explanation of the proposed research procedures in language that is appropriate to the child's age, experience, maturity, and condition. This explanation should include a discussion of any discomforts and inconveniences the child may experience if s/he agrees to participate.
- 3.2.3 While children may be legally incapable of giving informed consent, they may have the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether or not they wish to participate in the research, particularly if the research does not involve interventions likely to be of benefit to the subjects and they can comprehend and appreciate what it means to be a volunteer for the benefit of others.
- 3.2.4 When the IRB determines that assent is required, the Investigator (or his/her designee) and the child (when appropriate) will sign the study consent form to document that the subject has been given a verbal explanation of the proposed research in language that is appropriate to the child's age, experience, maturity, and condition. In other instances, the IRB may require that the Investigator develop a separate assent form. Such instances will be documented in the protocol file. When it is inappropriate to expect the signature of the child (due to age or ability) either on the consent form or the separate assent form, the IRB requires that the document be signed by the Investigator (or his/her designee) and the parent(s).
- 3.2.5 Waiver of Assent

The IRB may determine that assent is not necessary if:

- 3.2.5.1 The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- 3.2.5.2 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.

It should be noted that, in such circumstances, a child's dissent which should normally be respected, may be overruled by the child's parents at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening diseases such as cancer, however, the IRB should be sensitive

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to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

- 3.2.5.3 Even where the IRB determines that the child subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults. (See SOP 321: Waiver or Alteration of Informed Consent)

3.3 Permission of Parents or Legal Guardians

- 3.3.1 The IRB must find that adequate provisions are made for soliciting the permission of each child's parents, guardian or LAR. Although the regulations require the permission of each parent or guardian, there are circumstances in which the IRB may determine that permission from only one parent or guardian is sufficient. The following provisions apply based on the category of research in which the research falls:

- 3.3.1.1 **Research not involving greater than minimal risk to children.** Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research not involving greater than minimal risk.

- 3.3.1.2 **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child.** Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Important Note: Although the regulations allow permission of only one parent or guardian for research involving children which falls into categories 1 or 2 above, the IRB must determine that the permission of one parent or guardian is sufficient. The research falling into category 1 or 2 is not sufficient reason in and of itself. For example, it may be inappropriate to allow permission of only one parent or guardian in a standard therapeutic trial for childhood cancer where one has time to consult with, and obtain permission from, both parents (unless one is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child)

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just because the research falls into category 2.

3.3.1.3 **Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition.** When the research is approved under this category, and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

3.3.1.4 **Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.** When the research is approved under this category and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

3.3.2 Waiver of Parental or Legal Guardian Permission.

If the IRB determines that a research study is designed for conditions or for the subject population for which parental, or guardian or LAR permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children), it may waive the consent requirements. In order to protect the rights and welfare of the children, it may be appropriate for the IRB to consider the involvement of a court appointed guardian. Additionally, the requirement for parental permission may be inappropriate in cases involving older adolescents who, under applicable law, may consent on their own behalf for selected treatments (e.g., treatment for venereal disease, drug abuse, or emotional disorders).

3.4 Wards of the State or Other Agency

3.4.1 Children who are wards of the state or any other agency, institution, or entity are provided additional protections under the federal regulations. These additional protections for wards apply to two categories of research:

3.4.1.1 Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition (3.1.2.3 above); or

3.4.1.2 Research not otherwise approvable, which presents an

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opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (3.1.2.4 above).

3.4.2 Children who are wards of the state or any other agency, institution, or entity can be included in either of the above referenced research categories only if the IRB finds and documents that such research is:

3.4.2.1 Related to their status as wards; or

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

3.4.3 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 guardians 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 IRB Member) with the research, the investigators, or the guardian organization.

3.5 IRB Expertise When Reviewing Research Involving Children

3.5.1 An IRB considering a protocol involving children as subjects should:

3.5.1.1 Assess its needs for pediatric expertise among the voting IRB Members to assure that it possesses the professional competence necessary to review the specific research activities.

3.5.1.2 Consider inclusion of one or more individuals who are knowledgeable about and experienced in working with children. To fulfill this requirement, the IRB may invite nonvoting individuals to assist in the review of issues which require expertise beyond, or in addition to, that available among voting IRB Members.

4. RESPONSIBILITY

4.1 Investigator Responsibilities When Involving Children in Research

4.1.1 With any new study submission in which children will be a target population or may constitute some of the subject population, the investigator must obtain approval from the IRB before any children may be enrolled in the study.

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4.1.2 Additionally, within the protocol, plans should be described regarding if and how assent will be obtained and documented for IRB review and approval. Guidance on assent can be found in section 3.2 of this document.

4.1.2.1 In establishing this plan, the investigator should take into account the ages, maturity, and psychological state of the children. Although typically an assent would be appropriate, the following is also recommended:

4.1.2.1.1 Parental permission utilizing an informed consent document.

4.1.2.1.2 Ages less than 7 years: An oral script in very simple language appropriate for children in this age range.

4.1.2.1.3 Ages 7 to 12 years: An assent form written simply and at a comprehension level appropriate for children in this age range.

4.1.2.1.4 Ages 13 to 17 years: An assent form which may be in the same language as the adult consent document or the informed consent document itself with appropriate subject signature lines.

4.1.2.2 In situations where the potential benefits of the study are such that the investigator and parents will enroll the child regardless of the child's wishes, the child should simply be told what is planned and should not be solicited for his/her assent to participate. In such cases, the investigator should request a waiver of assent from the IRB.

4.1.2.3 If a waiver of assent has been approved by the IRB, the investigator will still obtain parental permission unless a waiver from parental permission has been granted.

4.1.2.4 The investigator may only approach the child to assent to the research study after the parents or legal guardians have given written permission.

4.2 IRB Responsibilities When Involving Children in Research

4.2.1 HRPP Support Staff is responsible for receipt of the protocol application submissions, entering it into the data management system, forwarding the request to a Protocol Analyst for administrative review, and notifying the Investigator of the submission's approval.

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- 4.2.2 Protocol Analysts are responsible for conducting administrative review of protocol application submissions, overseeing the review process for expedited review of eligible submissions, assigning protocols ineligible for expedited review to meeting agendas and overseeing the review process, recording meeting minutes into the data management system, ensuring findings are documented and generating correspondence
- 4.2.3 IRB Administrator in consultation with the IRB Chair and HRPP Director is responsible for establishing and implementing processes for conducting review of research. Additionally, s/he participates in the conduct of reviews in an ex-officio capacity for protocols reviewed by the convened IRB. If necessary s/he may conduct administrative reviews in lieu of an available Protocol Analysts or consult on administrative reviews.
- 4.2.4 IRB Chair or designee is responsible for providing consultation in the evaluation of protocol submissions, review revised protocol submissions in response to requests for revisions, and grant approval on behalf of the IRB. The IRB Chair or other experienced IRB Member designated by the IRB Chair to conduct expedited review are responsible for conducting and documenting the review and findings on the Protocol Review Form and special Review Form(s) as well as granting IRB approval of all submissions that qualify for expedited review. Additionally, they are responsible for determining the need for consultation with non-IRB Members.
- 4.2.5 IRB Members are responsible for participating in the review of protocol submissions reviewed at convened meetings.
- 4.2.6 Primary Reviewer is responsible for documenting the initial review and findings on the Protocol Review Form and, if applicable, special Review Form(s).
- 4.2.7 Institutional Official or his/her designee is responsible for conducting further appropriate review and granting Institutional approval.

5. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46, Subpart D, Additional Protections for Children Involved as Subjects in Research 21

CFR 50, Subpart D, Additional Safeguards for Children in Clinical Investigations

Indiana Code, Article 36, Medical Consent

6. REFERENCES TO OTHER APPLICABLE SOPs

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