The Christ Hospital IRB
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Number: 3.22
Effective Date: 04/12
Revision Date: 12/25

STANDARD OPERATING PROCEDURE

Additional Protections for Children Involved as Subjects in Research

1.0 PURPOSE

The purpose of this standard operating procedure is to describe regulatory and policy requirements that apply when a The Christ Hospital Institutional Review Board (IRB) is reviewing research involving children.

2.0 POLICY

The Christ Hospital requires that research includes additional safeguards to protect the rights and welfare of subjects when some or all the subjects are children. In addition to its other prescribed responsibilities, the IRB will review research involving children and approve only research which satisfies the applicable conditions as set out below. All research involving children, regardless of funding source, will be reviewed and approved in accordance with 45 CFR Part 46, Subpart D, as applicable.

3.0 DEFINITIONS

3.1 **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.

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

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

3.4 **Parent** means a child's biological or adoptive parent.

3.5 **Guardian** means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

4.0 OVERVIEW

4.1 Determining Applicability of Additional Protections for Children Involved as Subjects in Research (ref. 45 CFR Part 46, Subpart D)

The IRB may approve research involving children if the research falls into one of the following categories.

4.1.1 **Research Not Involving Greater Than Minimal Risk** (ref. 45 CFR 46.404) The IRB determines that both (1) the research involves no greater than minimal risk to children and (2) adequate provisions are made for soliciting the assent of the children and the permission of their parent(s) or guardian(s), as set forth in 45 CFR 46.408.

4.1.2 **Research Involving Greater Than Minimal Risk But Presenting the Prospect of Direct Benefit to the Individual Subjects** (ref. 45 CFR 46.405) The IRB determines that the research involves greater than minimal risk to child participants but that the research-related intervention or procedure holds out the prospect of direct benefit for the individual child participant, or by a monitoring procedure that is likely to contribute to the subject's well-being, and the IRB determines that all the following conditions are met:

4.1.2.1 The risk is justified by the anticipated benefit to the subjects;

4.1.2.2 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

4.1.2.3 Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

4.1.3 **Research Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge About the Subject's Disorder or Condition** (ref. 45 CFR 46.406)

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 participant, or by a monitoring procedure which is not likely to contribute to the well-being of the child participant, and determines all the following conditions are met:

4.1.3.1 The risk represents a minor increase over minimal risk;

4.1.3.2 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;

4.1.3.3 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

4.1.3.4 Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

4.1.4 **Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate A Serious Problem Affecting the Health or Welfare of Children** (ref. 45 CFR 46.407)

4.1.4.1 For HHS-funded research, if the IRB determines the research does not meet the review requirements or conditions of 45 CFR 46.404, 45 CFR 46.405 or 45 CFR 46.406, but 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, then the research will be referred to OHRP in accordance with 45 CFR 46.207.

4.1.4.2 For non-HHS-funded research, the IRB may approve the research if it determines that the research will be conducted in accordance with sound ethical principles and informed consent will be obtained in accordance with the informed consent provisions of 45 CFR 46, including all applicable subparts.

4.2 Determining Requirements for Permission by Parents or Guardians and for Assent by Children (ref. 45 CFR 46.408)

4.2.1 **Assent**

The IRB must 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.

4.2.1.1 In making this determination, the IRB must consider 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 appropriate.

4.2.1.2 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.

4.2.1.3 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 45 CFR 46.116.

4.2.2 **Parental/Guardian Permission**

4.2.2.1 When consent is required by 45 CFR 46.116, the IRB shall ensure that adequate provisions are made for soliciting the permission of each child's parents or guardian.

4.2.2.1.1 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 45 CFR 46.404 or 45 CFR 46.405.

4.2.2.1.2 Where research is covered by 45 CFR 46.406 and 45 CFR 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.

4.2.2.1.3 Permission by parents or guardians shall be documented in accordance with and to the extent required by 45 CFR 46.117.

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

4.2.2.2 When provisions for waiver of consent contained in 45 CFR 46.116 are met, if the IRB determines that a research protocol is designed for conditions or for a population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), it may waive the consent requirements provided an appropriate substitute mechanism for protecting the child research participants is put in place, and 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.

4.3 Considerations for Children Who are Wards (ref. 45 CFR 46.409)

4.3.1 Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 or 45 CFR 46.407 only if such research is:

4.3.1.1 Related to their status as wards; or

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

4.3.2 For research involving children who are wards, 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.

4.3.2.1 One individual may serve as advocate for more than one child.

4.3.2.2 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.

5.0 PROCEDURE

5.1 Principal Investigator or Authorized Designee

5.1.1 Creates a new protocol application through the web-based IRB submission system, Mentor IRB, and selects "Minors (under age 18)", indicating that children will be the target population for the research activities (refer to SOP 2.01, "Guidelines for New Protocol Submission" for submission guidelines);

5.1.2 Completes the section of the e-application addressing children as research participants; and

5.1.3 Addresses obtaining the informed consent process, assent process, and selection of participants, with particular attention to preventing undue influence or coercion.

5.2 IRB Chair/Primary Reviewer

5.2.1 Assesses whether the protocol meets the criteria for research involving children;

5.2.2 Reviews the protocol using the IRB Checklist to ensure that the required information to satisfy Subpart D for research activities involving children is sufficiently detailed;

5.2.3 Contacts the principal investigator and/or research coordinator with questions or needed clarification/documentation regarding the vulnerable population;

5.2.4 Assures that the IRB discusses and makes the required determinations under 45 CFR 46.404, 405, 406, and/or 46.408, when applicable; and

5.2.5 Reviews the IRB minutes to ensure that the following are sufficiently documented:

5.2.5.1 IRB discussion;

5.2.5.2 Any controverted issues;

5.2.5.3 Protocol-specific findings justifying waiver of the consent process or waiver of documentation of consent, as applicable; and

5.2.5.4 IRB determinations.

5.3 IRB Staff

5.3.1 Ensures that the submission is complete and is available in its entirety in Mentor IRB for IRB Chair or designee review (refer to SOP 2.01, "Guidelines for Protocol Submission" for document requirements);

5.3.2 Assigns the IRB Chair or designee as reviewer and assigns the "IRB: New Protocol Reviewer Checklist" to the reviewer;

5.3.3 Documents discussion and required determinations of the IRB in the minutes; and

5.3.4 Communicates all IRB determinations through Mentor IRB in a notification letter sent to the Principal Investigator and any research coordinator(s) as outlined in SOP 1.04, "Conducting IRB Meetings / IRB Meeting Minutes".

5.4 Convened IRB

5.4.1 Reviews the e-application assuring additional protections for children are included;

5.4.2 Reviews the proposed research, informed consent process, assent process and other applicable documents to determine whether the study meets criteria at 45 CFR 46.111 and 21 CFR 56.111, if applicable, for approval by the convened IRB;

5.4.3 Discusses the proposed research, taking into consideration additional requirements for children to participate in research described in 45 CFR 46, Subpart D; and

5.4.4 Issues approval only when all applicable sections of 45 CFR Part 46 Subparts A and D are satisfied.

5.4.5 If the convened IRB believes that the protocol is not approvable under the criteria above but finds that the research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, the IRB shall proceed according to the following procedures.

5.4.5.1 For research funded by HHS:

5.4.5.1.1 Refers the protocol to OHRP for a determination under 45 CFR 46.407(b);

5.4.5.1.2 Defers further action until a response is received from OHRP;

5.4.5.1.3 Reviews any changes proposed by OHRP through the response review process; and

5.4.5.1.4 Takes final action on the protocol at that time.

5.4.5.2 For research not funded by HHS:

5.4.5.2.1 Approves the research only if the IRB determines that:

5.4.5.2.2 The research is conducted in accordance with sound ethical principles, and

5.4.5.2.3 Informed consent will be obtained in accordance with 45 CFR 46.116 and all applicable additional subparts.

6.0 REFERENCES

6.1 IRB Standard Operating Procedures

6.1.1 2.01

6.1.2 1.04

6.1.3 3.04

6.2 Code of Federal Regulations

6.2.1 U.S. Department of Health and Human Services (HHS)

6.2.1.1 45 CFR 46

6.2.1.2 CFR Part 46 Subparts A and D

6.2.1.3 45 CFR 46.404

6.2.1.4 45 CFR 46.405

6.2.1.5 45 CFR 46.406

6.2.1.6 45 CFR 46.407

6.2.1.7 45 CFR 46.407(b)

6.2.1.8 45 CFR 46.408

6.2.1.9 45 CFR 46.409

6.2.1.10 45 CFR 46.111

6.2.1.11 45 CFR 46.116

6.2.1.12 45 CFR 46.117

6.2.2 U.S. Food and Drug Administration (FDA): 21 CFR 56.111

6.2.3 AAHRPP Domains and Elements: II.3.A, II.3.F, II.4.A, II.4.B