The Christ Hospital IRB
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IRB REFERENCE MANUAL
SECTION 06
VULNERABLE POPULATIONS

6.0 VULNERABLE POPULATIONS

The Christ Hospital IRB shall apply additional protections as necessary to protect research subjects, who could potentially be vulnerable to coercion in regard to autonomy, present conditions that may affect risk/benefit determinations, or bear unequal burden in research. Not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. The extent of additional protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations. In addition, when an IRB regularly reviews research involving a vulnerable population, consideration will be given to inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. Those groups or individuals who are recognized under federal law as having diminished autonomy entitling them to additional protection include minors, prisoners, and pregnant women, fetuses and neonates. (The Christ Hospital does engage in research involving prisoners.) References: The Belmont Report, 45 CFR 46.111(b), 21 CFR 56.111(b), 45 CFR 46 Subpart B, 45 CFR 46 Subpart C and 45 CFR 46 Subpart D

6.1 Pregnant women, fetuses and in-vitro fertilization: additional requirements for participation in research

6.1.1 Definitions

a. Fetus: product of conception from implantation until delivery
b. Dead fetus: fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord
c. Delivery: complete separation of the fetus from the woman by expulsion or extraction or any other means
d. Neonate: newborn

e. Viable: as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration
f. Nonviable neonate: a neonate after delivery that, although living, is not viable
g. Pregnancy: encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery

6.1.2 General requirement for research involving pregnant women and fetuses (45 CFR 46.204, Subpart B)

Pregnant women or fetuses may be involved in research only if all the following conditions are met:

a. Where scientifically appropriate, preclinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
b. The risk to fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
c. Any risk is the least possible for achieving the objectives of the research.
d. The informed consent of the pregnant woman shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit to both the pregnant woman and the fetus, or no prospect of direct benefit for the pregnant woman nor fetus when the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means.
e. The informed consent of the pregnant woman and the father shall be obtained in accord with the standard regulatory provisions for informed consent if the research holds out the prospect of direct benefit solely to the fetus; except the father's consent need not be obtained if he is unable to

consent because of unavailability, incompetence, or temporary incapacity, or if the pregnancy resulted from rape or incest.

f. Each individual providing consent under 4) or 5) above shall be fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
g. No inducements, monetary or otherwise, shall be offered to terminate the pregnancy.
h. Individuals engaged in the research shall have no part in any decisions as to the timing, method or procedures used to terminate a pregnancy.
i. Individuals engaged in the research shall have no part determining the viability of the neonate.

6.1.3 General requirements for research involving neonates (45 CFR 46.205, Subpart B)

a. Neonates of uncertain viability and nonviable neonates may be involved in research only if all the following conditions are met:

    1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
    2) Each individual providing consent (see b.2 and c.5 below) is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
    3) Individuals engaged in the research will have no part in determining the viability of the neonate.
    4) The requirements outlined under this section, items (b.) and (c.) below, have been met as applicable.

b. Requirements for research involving neonates of uncertain viability: Until it has been determined whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions are met:

    1) The IRB determines that:

        i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for

achieving the objectives of the research, or

ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the standard regulatory provisions for informed consent; except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. (NOTE: For research involving viable neonates, the IRB is permitted to grant a waiver or alteration of such informed consent in accord with applicable regulatory provisions.)

c. Requirements for research involving nonviable neonates: A nonviable neonate may not be involved in research unless all the following additional conditions are met:

1) Vital functions of the neonate will not be artificially maintained.
2) The research will not terminate the heartbeat or respiration of the neonate.
3) There will be no added risk to the neonate resulting from the research.
4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.
5) The legally effective informed consent of both parents of the neonate is obtained in accord with the standard regulatory provisions for informed consent. However, the IRB is not permitted to grant a waiver or alteration of such informed consent for (1) research involving nonviable neonates, and (2) the consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to

meet the requirements of this paragraph. If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph; except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest.

d. Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

6.1.4 General requirements for research involving, after delivery, the placenta, the dead fetus or fetal material (45 CFR 46.206, Subpart B)

a. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
b. If information associated with the dead fetus; macerated fetal material; or cells, tissue or organs excised from a dead fetus is recorded in such a manner that living individuals (e.g., the parent(s)) can be identified, directly or through identifiers linked to such individuals, those individuals are "human subjects" of the research study and the requirement for their informed consent applies.

6.1.5 General requirements for research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates (45 CFR 46.207, Subpart B)

Research the IRB does not believe meets the requirement of sections 6.1.2, 6.1.3 or 6.1.4 may be approved 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 and welfare of pregnant women, fetuses or neonates; and
b. The Secretary, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law)

and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

1) The research in fact satisfies the conditions of sections 6.1.2, 6.1.3 or 6.1.4, 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 pregnant women, fetuses, or neonates;
   ii. The research will be conducted in accord with sound ethical principles; and
   iii. Informed consent will be obtained in accord with the standard regulatory provisions for informed consent unless the IRB has approved a waiver or alteration of the standard informed consent requirements.

6.2 When subjects become prisoners during a research protocol

The Christ Hospital does not engage in research involving prisoners. If a subject becomes a prisoner after enrollment in research, the Principal Investigator is responsible for reporting this in writing to the IRB immediately. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease ***and the subject must be withdrawn from the study***.

In special circumstances in which the PI asserts that is it in the best interests of the subject to remain in the research study while incarcerated, or feels that withdrawal from the study presents significant risks to the patient, the IRB Chair may determine that the subject may continue to participate in the research until the requirements of HHS regulations at 45 CFR part 46, Subpart C, "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" are satisfied.

At the earliest opportunity after receiving the Principal Investigator's recommendation to allow the subject to remain in the study, the IRB should review the protocol again with a legal representative from the hospital's Risk Management Department. The Committee should take special consideration of the conditions of being a prisoner as set forth in 45 CFR

46, Subpart C. Upon this review, the IRB can either a) approve the involvement of the prisoner-subject in the research in accordance with this policy or b) determine that this subject must be withdrawn from the research. Additionally, the IRB should confirm that, when appropriate, the informed consent process includes information regarding when subsequent incarceration may result in termination of the subject's participation by the investigator without regard to the subject's consent.

6.3 Other vulnerable groups

Although the federal regulations do not list all vulnerable groups, the IRB considers vulnerable groups to include: mentally impaired or disabled persons; employees of the sponsor or investigator or The Christ Hospital; terminally ill patients; and the very elderly. The IRB will determine special protections for these groups on a case-by-case basis, taking into account the risks and benefits and other protections afforded by institutional policies and state and federal law.

6.3.1 Adults with impaired decision-making capacity

Decisionally impaired adults are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals may be considered decisionally impaired or have limited decision-making ability because they are under the influence of or dependent on drugs or alcohol, suffering from degenerative diseases affecting the brain, are terminally ill or have severely disabling physical handicaps.

There are no regulations specific to research involving adults with impaired decision-making capacity. The IRB takes special care to consider issues such as the selection of participants, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions should be made with the utmost deference to the ethical principles underlying human research as set forth in the Belmont Report.

The National Bioethics Advisory Commission (NBAC) has issued 21 recommendations for IRBs, the research community, and Federal regulators to consider regarding the decision-making capacity of particularly vulnerable subjects.

The following criteria should be taken into consideration for adult participants with impaired decision-making capacity involved in a research protocol:

a. The objectives of the research cannot be met by conducting the research in a population that does not have the disorder that may affect decision-making capacity.
b. The research is designed for a disease or condition relevant to the vulnerable population under study.
c. The research is either minimal risk, more than minimal risk with a prospect of direct benefit, or more than minimal risk without a prospect of direct benefit, but of vital importance to the vulnerable population.
d. Adequate provisions are made for obtaining consent from the participant's legally authorized representative.
e. Adequate provisions are made for obtaining assent from the participant, unless the IRB determines that assent is not appropriate as a condition of participation or that some or all participants are not capable of providing assent.
f. The protocol must describe when and how the participants will be assessed for capacity for formal consent or assent and understanding of the proposed research, and the process for a second confirming assessment. Competency should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. Criteria for determining competence might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gain can be anticipated.

The IRB will consider additional safeguards to protect participants. Such decisions may be based on the amount of risk involved in the research and the likelihood that participants will derive health benefits from their participation. These include:

a. Requiring the involvement of participant advocates
b. Requiring independent monitoring
c. Requiring waiting periods
d. Appointing a monitor to supervise the informed consent process

6.4 Additional protections for children involved as subjects in research

When a proposed research study involves children and is supported or conducted by HHS, the IRB must take into consideration the special regulatory requirements that provide additional protection for the children who would be involved in the research. If the proposed research involves FDA-regulated products, then FDA's parallel regulations apply.

When reviewing research with children as subjects, in addition to ensuring adherence to the general regulatory requirements of 45 CFR part 46, Subpart A, the IRB also must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risks and potential benefits, the IRB should consider the circumstances of the children to be enrolled in the study; for example, their health status, age, and ability to understand what is involved in the research, as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole.

6.4.1 Definitions

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.

6.4.2 Risk/benefit categories

The IRB considers the following risk/benefit categories when evaluating research involving children for approval:

a. Research not involving greater than minimal risk (Minimal Risk)
b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants
c. Research involving greater than minimal risk and no prospect of direct benefit to individual participants but likely to yield generalizable knowledge about the participant's disorder or condition
d. Research not otherwise approvable through categories (a.) through (c.) above

Risk Category	Risk Level	Provisions
a. Research not involving greater than minimal risk (45 CFR 46.404 and 21 CFR 50.51)	The risks of the research are no more than minimal.	• Permission from one parent/guardian may be sufficient, unless the requirement to obtain parental/guardian permission is waived. • Adequate provisions are made for soliciting the assent of child- participants, unless the requirement to obtain child assent is waived. (Ref. §46.408)
b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects (45 CFR 46.405 and 21 CFR 50.52)	• More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject or by a monitoring procedure that is likely to contribute to the subject's well-being; • The risk is justified by the anticipated benefit to the subjects; and • The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches.	• Permission from one parent/guardian may be sufficient, unless the requirement to obtain parental/guardian permission is waived. • Adequate provisions are made for soliciting the assent of child- participants, unless the requirement to obtain child assent is waived. (Ref. §46.408)
c. Research involving greater than minimal risk and no prospect of direct benefit to individual participants but likely to yield generalizable knowledge about the participant's disorder or condition (45 CFR 46.406 and 21 CFR 50.53)	• 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 participant, or by a monitoring procedure that is not likely to contribute to the well-being of the child; • The risk represents a minor increase over minimal risk; • The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and,	• Permission from both parents or guardians, unless: a. one parent is deceased, unknown, incompetent, or not reasonably available, or b. when only one parent has legal responsibility for the care and custody of the child, c. the IRB waives the requirements for obtaining parental or guardian permission. • Assent of child participants, unless the requirement to obtain child assent is waived.

	• The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition.	• Enrolling wards of the state or any other agency, institution, or entity (e.g., orphans) with the appropriate documentation that: a. Recognizes the status of the individual child as a ward; b. Ensures communication of that status to the IRB; and c. Confirms the IRB appointment of an advocate for the child/ward, in addition to any other individual acting as guardian or in loco parentis. Ref. 45 CFR 46.409 and 21 CFR 50.56 for additional information on the role of the advocate.
d. Research not otherwise approvable (45 CFR 46.407 and 21 CFR 50.54)	This category designation is only given for research which does not meet the conditions under 45 CFR 46.404, 46.405, or 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.	• 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 including adequate provisions for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408. • Research also subject to FDA regulations under 21 CFR 312 (or 812), FDA regulatory requirements at 21 CFR 50.54 must be met.

6.4.6 Requirements for permission by parents or guardians assent by children (Ref. 45 CRF 46)

a. In addition to the determinations required under other applicable sections of RM 06, 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 45 CFR 46.116 of Subpart A.

b. In addition to the determinations required, the IRB shall determine, in accordance with and to the extent that consent is required by 45 CFR 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 45 CFR 46.116, 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 and paragraph 6.4.6(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, Subpart A.

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

6.4.7 Wards (Ref. 45 CFR 46.409)

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 investigators(s), or the guardian organization.