

Special Considerations: Children	
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1. PURPOSE

- 1.1. Federal regulations require that research involving “vulnerable” populations such as children be reviewed under 45 CFR 46 subpart D. “Vulnerable” in the context of human subjects research protections does not refer to the susceptibility of harm, but rather the inability or a threat to the ability of an individual to give voluntary informed consent. When some or all the subjects are likely to be vulnerable to coercion or undue influence, the IRB must ensure that additional safeguards are in place to protect the rights and welfare of these subjects.

2. DEFINITIONS

- 2.1. *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.
(*Note:* In California, the legal age for such consent is usually 18 years old, but some exception apply under the state law. These or applicable laws of other states or countries where the research is being conducted will be considered by the IRB.)
- 2.2. *Assent*, means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- 2.3. *Permission*, is the agreement of the parent(s) or guardian to the participation of their child or ward in research.
- 2.4. *Parent*, is a child’s biological or adoptive parent.
- 2.5. *Guardian*, means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

3. POLICY and PROCEDURE

Inclusion of Children in Research

- 3.1. Enrolling children in research may present difficult considerations for the IRB. Several factors make a case for inclusion in research:
 - A. Children differ markedly from both animals and adults, and therefore, these models cannot substitute as alternatives to testing or gathering information from children.
 - B. Lack of appropriate research in children could increase their risk of harm from exposure to practice or treatments untested in this populations, and optimal therapies could not be developed for diseases or conditions that specifically affect children.

Risk and Benefits Determination

- 3.2. Research with children requires that the IRB give careful consideration to special issues related to the risk/benefit ratio and consent. Therefore, the IRB must consider the degree of risk and any discomfort (real or perceived) in the research in relation to the direct benefits it offers to the child before it can determine whether or not the IRB has the authority to approve the study.
- 3.3. Federal regulations at 45 CFR 46, subpart D include four categories of permissible research with children. Risk is defined in terms of minimal and greater than minimal risk, and may only be approved by the IRB if it finds that:

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- 1) 45 CFR 46.404 - Research not involving greater than minimal risk to the children if:
 - a) The research presents no greater than minimal risk to the children; and
 - b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
 - 2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child involved in the research if:
 - a) The risk is justified by the anticipated benefits to the subjects;
 - b) The relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; and
 - c) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.
 - 3) 45 CFR 46.406 - Research involving greater than minimal risk with no prospect of direct benefit to the individual child involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition if:
 - a) The risk to the research represents a minor increase over minimal risk;
 - b) The intervention or procedure presents experiences to the subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations;
 - c) The intervention or procedures is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and
 - d) Adequate provisions are made for soliciting assent of the children and the permission of their parents or guardians.
 - 4) 45 CFR 46.407 - Research that may not otherwise be approvable under 1-3 above, but 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, it may refer the protocol to HHS for review. The research may proceed only if the Secretary, HHS, or designee, after consulting with a panel of experts in pertinent disciplines (e.g. science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: 1) that the research in fact satisfies the conditions items 1-3 above (i.e. 45 CFR 46.404, 46.405, 46.406) or 2) the following:
 - a) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - b) The research will be conducted in accordance with sound ethical principles; and
 - c) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as described in 45 CFR 46.408.
- 3.4. In addition to the above determinations, 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 1-2 above (i.e 45 CFR 46.404 or 46.405). Where research is covered 3-4 above (45 CFR 46.406 or 46.407) and permission is to be obtained from parents, both parents must

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give their permission unless one parent is deceased, unknown, incompetent, or reasonably unavailable, or when only one parent has legal responsibility for the care and custody of the child.

Wards

- 3.5. Children who are wards of the state or any other agency, institution, or entity can be included in the research approved under items Section 3.3, 1-2 above only if such research is:
- a) Related to their status as wards; or
 - b) Conducted in schools, campus, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.
- 3.6. If the research is approved under Section 3.5 above, the IRB will require an appointment of advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as a 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 interest 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.

Child Assent and Waiver of Child Assent

- 3.7. The process of asking a child to participate in research should be carefully planned and implemented, using age-appropriate language and methods, for any child who is considered capable of understanding and providing assent. This process should include a clear explanation (verbally, and in written form when applicable) that conveys:
- What the study is about;
 - Why the child is eligible/being invited to participate;
 - Procedures the child will be expected to take part in;
 - Potential risks and/or discomforts to the child;
 - Potential benefits to the child or society;
 - That the child is completely free to choose whether or not to participate, and may withdraw at any time without any negative consequences
 - An invitation to ask questions at any time;
 - Names and contact information of whom to contact with questions
- (*Note:* Assent language *must* be tailored to the reading and comprehension level(s) of the subject populations to be enrolled and will vary widely from study to study. When verbal assent only is proposed, an *assent script* (containing some/all of the elements listed above) may be advised.)
- 3.7.1. Multiple methods of explaining the study should be used as suitable (e.g., videotapes, online presentations, written materials, diagrams, etc.) Younger children are likely to understand verbal explanations better if they are accompanied by concrete examples that the child can relate to past experience.

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Each child, if capable, should have the opportunity to sign an assent form and take a copy home to review later.

- 3.7.2. The federal regulations do not recommend that assent be sought starting at a specific age (although California law requires assent for experimental medical procedures "if the subject is seven years of age or older" [CA Health & Safety Code §111530]). The IRB agrees that, in most cases, seven years of age is a reasonable minimum for a child with normal cognitive development to be capable of participating in a meaningful written assent process, and that many adolescent minors (13 to 17 year olds) will be able to participate in a written assent process that is similar to that of adult consent.
 - 3.7.3. Dissent of a child (i.e., their actual objection to research) should be considered binding, especially in non-therapeutic research. (There are rare exceptions, e.g., where a study may offer direct medical benefit to a younger child).
 - 3.7.4. If the child is considered capable of being involved in the informational process (regardless of age), at least a simple verbal explanation of what will happen to him/her and the opportunity for questions and discussion should be given. Even if the requirement for assent is *waived, it is always preferable to involve the child in the process as much as possible.*
 - 3.7.5. There must be documentation on the parent permission form and/or in the study records that the child was informed about the study.
- 3.8. The IRB may decide whether child assent is required in a proposed research project and will require child assent unless it determines that the research satisfies one of the conditions as described in 45 CFR 46.408:
- a) The capability of some or all of the children is so limited that they cannot reasonably be consulted;
 - b) 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.
- 3.8.1. The IRB may still waive the assent requirements under circumstances in which consent may be waived for adults under 45 CFR 46.116(c):
- Waiver Criteria under 45 CFR 46.116(c):**
- 1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
 - 2) The research could not practicably be carried out without the waiver or alteration.
- Waiver Criteria under 45 CFR 46.116(d):**
- 1) The research involves no more than minimal risk to the subjects;

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- 2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- 3) The research could not practicably be carried out without the waiver or alteration; and
- 4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(*Note:* Investigators must provide justification/rationale, based on one of the criteria above in the ORahs protocol application for IRB review).

Parental Permission and Waiver of Permission

3.9. In most instances, the IRB expects that the parent(s) will play a vital part in the consent process for research involving their child. The investigator should make every effort to assure that both the parents and child understand the research, and their respective rights, as thoroughly as possible. This includes conveying to parents that they should respect their child's autonomy in this regard (e.g., not exert overt or implied pressure for the child to participate, not indicate anger or disappointment if the child wishes to decline or withdraw from the study). Usually, the parent(s) must be provided with a permission form that meets all requirements for adult consent, but is written to refer to the subject as "your child" instead of "you."

3.9.1. If there are two parents available to give permission and the researcher becomes aware that they disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. (This applies to all permissible categories; i.e., even if only one parent's signature is required, when both parents are involved in the decision, they must agree in order for the child to participate).

3.10. The IRB may waive the requirements for obtaining parent or guardian permission for research involving children if either of the sets of conditions is met:

- a) Under 45 CFR 46.116(c) or 46.116(d) (Section 3.8.1 above)
- b) Under 45 CFR 46.408:
 - The IRB may waive the requirement for permission if it finds that "a research protocol is designed to study conditions in children or a subject population for which parent or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children)." Research on neglected or abused children is one example for possible waiver; the IRB interprets this regulation as also applying to people under 18 years of age who are in circumstances where they are clearly outside of parental influence or control (though not legally able to consent for themselves). The IRB will evaluate each waiver request carefully to determine if "parent or guardian permission is not a reasonable requirement to protect the subjects" in that case.
 - To grant any waiver under 45 CFR 46.408, the IRB must also find that: "(i) an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted; and... (ii) the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism [will]

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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."

Documentation of Assent and Permission

3.11. Parent permission must be documented as required for adult consent. For child assent, the IRB recommends the following general guidelines for permission and assent by age group of the child subject and documentation thereof:

a) Children up to 7 years old: Children in this age range may not be able to participate in a written assent process, or if very young or otherwise incapable, in any meaningful assent process. In such cases, only a permission form for the parents will be required. This form should be adapted from the UCSB HSC template parent permission forms.

(*Note:* In many cases, the investigator may deem a child younger than 7 years old capable of being involved in the assent process. If so, the investigator should make sure that the child is given a simple explanation of what will happen to him/her, and that there is documentation on an assent form/script, the parent permission form, or in the study records that this was done.)

b) Children 7 to 12 years old: In most cases, children this age will be able to participate in the assent process using a simplified assent form. The child should sign the form if possible. If not, the form or study records must still document that verbal assent was obtained.

c) Adolescents 13 to 17 years old: In most cases, adolescents should be fully informed about a study and give signed assent to their own participation in the research.

(*Note:* In some cases, e.g. where the parent permission form will be identical in content to the adolescent assent form, the investigator may propose using one form, with signature lines for the adolescent's assent followed by the parent's permission.)

4. SCOPE

These policies and procedures apply to all human subjects research conducted by investigators affiliated with UCSB.

5. RESPONSIBILITY

The investigator is responsible for ensuring appropriate procedures for obtaining informed consent are followed when obtaining child assent and parental permission. The investigator is responsible for requesting a waiver of consent when certain circumstances are met.

The IRB staff are responsible for an initial review of all new and continuing research protocol applications as described in HSC SOPs 014 and 017 – *Initial Review* and *Continuing Review*.

The IRB staff and Research Integrity Office are responsible for ensuring that IRB members are apprised of new and evolving regulations and guidelines pertaining to vulnerable

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populations, for selecting discussion leaders with appropriate expertise to conduct the reviews of such research.

The IRB reviewers are responsible for conducting an appropriate review of research planned for vulnerable populations, including an assessment of potential coercion, in consultation with any appropriate experts and resources as needed.

6. PROCESS OVERVIEW

- 6.1. Proposed research involving vulnerable populations must take special precautions to ensure that the research participants' rights, safety, and welfare are safeguard against any risks.
- 6.2. IRB members must take in consideration subpart D of the federal regulations and any other applicable federal, state, or local laws when reviewing research involving children.
- 6.3. When evaluating the proposed research, the IRB members will ensure that the protocol contains the appropriate informed consent processes and will identify any additional potential risks and safeguards needed to protect the participants' rights, safety, and welfare.
- 6.4. The IRB staff will communicate any requests for revisions or clarifications requested by the IRB before final approval of the research application.

References:

45 CFR 46 Regulations
 UC Berkeley Policies and Procedures
 Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects Research