P&P: SC 503 Version No: 1.1 Effective Date: 10/1/2009	CHILDREN AS A VULNERABLE POPULATION	Supercedes: CPHS Policies and Procedures 9/1/2007

1. POLICY

The use of the term "vulnerable" in the context of human research protections does not refer to 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 subjects are likely to be vulnerable to coercion or undue influence the IRB must ensure that additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Special ethical and regulatory considerations apply when research involves children as subjects. The three main principles elucidated in The Belmont Report and codified in federal research regulations—respect for persons (autonomy), beneficence, and justice—must be balanced in appropriate ways. Children are inherently more vulnerable than adults, requiring a higher level of protection in research. At the same time, the IRB has the responsibility to assure equitable selection of children as research participants, so that they may receive a rightful share of the benefits of research. Since children are legally incapable of giving valid informed consent, provisions also must be made regarding assent by the child or minor and/or permission of the parent(s) or guardian (see IC 103, "Assent and Parental/Guardian Permission"). The IRB will apply the requirements and guidance found in federal regulations 45 CFR 46, Subpart D, "Additional Protections for Children Involved as Subjects in Research," to evaluate any research involving children as participants.

Specific Policies

1.1 **Definitions** (as per federal regulations at 45 CFR 46.402)

1.1.1 *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 exceptions apply under state law (see below). These or applicable laws of other states or countries where the research is being conducted will be considered.

"Children" vs. "Minors": Under California law, both terms—"children" and "minors"—are used to refer to people who are under 18 years of age. However, some people under 18 years of age can consent for themselves to certain research procedures (e.g., self-sufficient minors, emancipated minors, those seeking medical care related to the prevention or treatment of pregnancy). Therefore, not all "minors" meet the federal criteria for being "children" (*as defined above*). Only people who are "children" under the federal regulations are covered by the additional protections described in Subpart D of 45 CFR 46 and 21 CFR 50. *Thus, these policies and procedures will be applied in all cases involving minors who are also considered "children" under the federal regulations. In some cases, the IRB may choose to apply them to minor subjects who are not considered children under the federal definition as well, depending on the specific research.*)

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

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

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

1.1.5 *Guardian* means an individual who is authorized under applicable State or local law to consent on before of a child to general medical care.

1.2 Inclusion of Children in Research

1.2.1 Enrolling children in research, especially clinical research, may present difficult considerations for IRBs. Several factors make a case for such inclusion:

- Children differ markedly from both animals and adults, and therefore, these models cannot substitute as alternatives to testing or gathering data from children.
- Lack of appropriate research in children could increase their risk of harm from exposure to practices/treatments untested in this population, and optimal therapies could not be developed for diseases/conditions that specifically affect children.

However, research with children requires that the IRB give careful consideration to special issues related to risk/benefit ratio and consent.

1.3 Determination of risks vs. benefits

1.3.1. The IRB must consider the degree of risk and discomfort involved 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.

Federal regulations 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 as follows:

1) **45 CFR 46.404 -** Research not involving greater than minimal risk to the children/ subjects, if:

- the research presents no greater than minimal risk to the children; *and*
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

2) **45 CFR 46.405 -** Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child/subject involved in the research, if:

- the risk is justified by the anticipated benefits to the subjects;
- 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*
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

3) **45 CFR 46.406 -** Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition, if:

- the risk of the research represents a minor increase over minimal risk;
- 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;
- the intervention or procedure 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
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

4) **45 CFR 46.407 -** Research that the IRB believes does not meet the conditions of 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.

   If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but finds that it 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 his or her 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 of 45 CFR 46.404, 46.405, or 46.406, or (2) the following:
   - 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*
   - adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

1.3.2 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 45 CFR 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.

1.4 Wards

1.4.1 As per 45 CFR 46.409, 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.

1.4.2 If the research is approved under paragraph 1.4.1 of this section, the IRB will 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.

1.5 For any research involving children, the IRB shall determine requirements for obtaining assent from the children/subjects and/or permission from their parent(s)/ guardian (see IC 703, "Assent and Parental/Guardian Permission").

2. SCOPE

These policies and procedures apply to all research submitted to the UC Berkeley IRB.

3. RESPONSIBILITY

The IRB Manager is responsible for maintaining up-to-date review tools for review of research pertaining to vulnerable groups based on new and evolving applicable regulations and guidelines.

The IRB Chair and/or the OPHS Director is responsible for ensuring the IRB members are well versed in new and evolving regulations and guidelines pertaining to vulnerable populations, for selecting primary reviewers with appropriate expertise to conduct the reviews of such research, and for securing appropriate consulting expertise as needed for selected reviews.

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

4. PROCESS OVERVIEW

When proposed research involves vulnerable populations, the IRB must take special precautions to ensure research participants' rights, safety, and welfare. In all cases involving vulnerable populations, the IRB Chair(s) and members must be cognizant of the subjects' needs when evaluating the protocol and are responsible for determining any additional protective stipulations to be applied to the research.

When proposed research involves children, OPHS staff, IRB Chair(s), and IRB members will ensure that the protocol contains consent, permission, and/or assent documents as appropriate.

5. APPLICABLE REGULATIONS AND GUIDELINES

The Belmont Report

45 CFR 46: Subpart D

45 CFR 46.122

21 CFR 56.111

NIH Policy on Inclusion of Children in Research (March 1998)

OHRP IRB Guidebook