CHILDREN IN RESEARCH

This guidance document is intended for investigators who plan to conduct research involving children as subjects. (Also see CPHS Guidelines on Child Assent and Parent Permission.) Should you need additional assistance, please contact OPHS at 510-642-7461 or ophs@berkeley.edu.

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A. Introduction

Special ethical and regulatory considerations must be considered when research involves children as subjects. Children are inherently more vulnerable than adults, requiring a higher level of protection in research. In keeping with the principles elucidated in the Belmont Report, the CPHS is responsible for assuring that selection of children as research participants is equitable, that possible benefits outweigh risks of harm, and that benefits are maximized and risks minimized. Moreover, because children are legally incapable of giving valid informed consent, the Committee must assure that adequate provisions are made regarding assent of the child and permission of the parent(s) or guardian(s).

In reviewing such studies, the CPHS will apply the requirements found in federal regulations 45 CFR 46, Subpart D, "Additional Protections for Children Involved as Subjects in Research" (and 21 CFR 50: Subpart D, the corresponding regulations of the FDA), as well as pertinent state and local regulations. Relevant Policies & Procedures of the CPHS can be found on our website under SC-503: Children as a Vulnerable Population and IC-703: Assent and Parent/Guardian Permission.

Issues related to permissible research with children are discussed below. *For complete topic information (including assent of children in different age ranges), be sure to see companion CPHS guidance on* Child Assent and Parent Permission.

B. Definitions

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." (See Section D, pt. 1 below for further discussion on this topic, including definitions of "children" vs. "minors.")

   [***Note***: In this document, unless otherwise specified, the terms "child(ren)" and "minor(s)" both refer to the definition above.]

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

   [***Note***: In this document, the term "child" is used in place of "child/ward."]

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

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."

   [***Note***: For the remainder of this document, the term "parent(s)" is used in place of "parent(s)/guardian(s)"].

C. Permissible Research with Children

1. Federal regulations **include four categories of permissible research with children**, based on the study's risks-benefits ratio. Risk is defined in terms of *minimal risk* and *greater than minimal risk*. Research with children may only be approved by the IRB if it finds that the study fits within Category 1, 2, or 3; if it fits Category 4, the IRB may proceed as specified below. (See ***Categories of Permitted Research with Children*** table, pt. 2.)

   -*Minimal risk* is defined as: "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 or during the performance of routine physical or psychological examinations or tests." [45 CFR 46.102]

   -*Greater than minimal risk* is a term used in defining Category 2 [45 CFR 46.405] and Category 3 [45 CFR 46.406]. The regulations do not provide any additional definition of this term (except for indicating that risk must be no more than "a minor increase over minimal risk" in regards to Category 3). The CPHS will thus determine in which category a study belongs on a case-by-case basis.

2. ***Categories of Permitted Research with Children***

1) Minimal Risk [45 CFR 46.404] ▪ *Description*: Research not involving greater than minimal risk to subjects. ▪ *Requires*: Permission of ONE parent/guardian. ▪ *Type of review needed*: Expedited review (in most cases).
2) Greater than Minimal Risk, Direct Benefit to Subject [45 CFR 46.405] ▪ *Description*: Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. ▪ *IRB must find:* 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. ▪ *Requires*: Permission of ONE parent/guardian. ▪ *Type of review needed*: Full Board review by CPHS.
3) Greater than Minimal Risk, No Direct Benefit to Subject, but Likely to Yield Generalizable Knowledge about Subject's Condition [45 CFR 46.406] ▪ *Description:* 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. ▪ *IRB must find*: The risk of the research represents a minor increase over minimal risk; the intervention or procedure presents experiences to the child 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.

- *Requires*: Permission of BOTH parents/guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.
- *Type of review needed*: Full Board review by CPHS.

4) Greater Than Minimal Risk, No Direct Benefit to Subject, Not Approvable Under Other Categories, But Results May Alleviate Serious Problems of Children's Health or Welfare [45 CFR 46.407]
NOTE: A Category 4 study is very rarely approved.

- *Description:* The research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but appears to present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
- *IRB must find:* If the IRB makes the above determination, it may refer the protocol to HHS.
- *Requires:* The Secretary of the US Department of Health and Human Services, after consultation with a panel of experts and following an opportunity for public review and comment, must either approve or deny approval of the study.
- *Requires:* Permission of BOTH parents/guardians, unless one parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the custody of the child.
- *Type of review needed:* Full Board review by CPHS *and review by DHHS as above.*

Note: Investigators should be aware of the above categories and include all relevant information in their applications to assist the CPHS in making determinations in this regard (e.g., what category the research falls under, whether suitable provisions are made for obtaining parent permission, etc.)

D. Special Considerations

1. *"Children" versus "Minors" in Research*

In most states in the U.S., including California, 18 is the age of majority. However, under certain circumstances and in certain states, youth who are under 18 years of age can consent to research for themselves without parent permission. Thus, not all "minors" meet the federal criteria for being "children" (as defined in §46.402, above).

For example, California law (see California Family Code) permits some minors to consent to research, including:

- Emancipated minors (CFC Sec. 7000-7143)
- Self-sufficient minors (CFC Sec. 6922)
- Minors seeking care related to the prevention or treatment of pregnancy (CFC Sec. 6925)
- Minors, 12 years or older, seeking care for other specified conditions (CFC Sec. 6929).

The California Family Code (CFC) includes more restrictions and exceptions than can be summarized here. Investigators considering enrolling such individuals and arguing for these subjects' *consent* rather than *assent* should reference applicable sections of the law in their submissions.

Note: In general, investigators should be aware of and include relevant information in their CPHS applications about laws regarding "children" or "minors" in California or other states or countries where the research is being conducted. (For further information about research in other countries, see CPHS Guidelines on Research in an International Setting.)

Although only people who are "children" under the federal regulations are covered by the additional protections described in Subpart D of 45 CFR 46, the CPHS may choose to apply these protections to minor subjects not considered children under the federal definition.

2. ***Wards***

- Per 45 CFR 46.409, children who are wards of the state or any other agency, institution, or entity can be included in any research approved under §46.404 or §46.405, but 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.

- If the research is approved under §46.406 or §46.407, 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.

3. ***Discovery and Reporting of Sensitive Information***

In the course of research with minors, especially adolescents, investigators may discover sensitive information about subjects that is not related to the study itself. Examples of such information include sexual activity, STDs, use of illegal substances, HIV status**,** and child abuse**.**

Confidentiality: Investigators need to consider how they will handle such situations should they arise. The permission and/or assent form should describe plans for disclosure—or non-disclosure—of such information to parents, legal authorities, and the subjects themselves.

- In some cases, it may be appropriate for the PI to seek an *NIH Certificate of Confidentiality*. (See http://grants.nih.gov/grants/policy/coc/background.htm for information as to whether this is applicable for a particular study).

- As with all consent forms, a promise of complete confidentiality should never be given or implied. (See CPHS Informed Consent Guidelines and sample consent forms for recommended wording.)

Child Abuse Reporting: Ethical and legal obligations apply whenever child abuse is discovered. Investigators should be aware that, in most cases, the same reporting expectations pertain in research settings as in clinical settings. University researchers may fall into a category of health professionals or others listed as "*mandated reporters*" under the California Child Abuse and Neglect Reporting Act (CANRA) (California Penal Code 11164-11174.4).

Based on the CANRA, the University of California Office of the President (UCOP) issued its Policy on Reporting Child Abuse and Neglect, effective March 17, 2015. See CPHS guidelines on Mandated Reporting for Suspected Child, Elder, or Dependent Adult Abuse or Neglect for relevant information, consent form wording, etc. in this regard.

Even if the mandated reporter status is not clear, the researcher can make a voluntary report to the appropriate agency.

- If an investigator is planning a study that is designed or likely to elicit information about sexual or physical abuse of a child, the application and consent/assent/permission forms must indicate how

discovery of such information will be handled, including reference to the Mandated Reporting guidelines (above) as applicable.

- If such information is discovered unexpectedly (i.e., not anticipated given the study design or subject population), the PI should seek advice from his/her department chair or dean or from the director of the OPHS, who may refer the question to UC legal counsel.

4. ***Pregnancy Testing for Minor Girls***

Special protections are needed when research involves MRI (magnetic resonance imaging), fMRI (functional MRI), MRS (magnetic resonance spectroscopy), or similar procedures and/or drugs where the effects on a fetus are unknown. Provisions may be required for screening to assure that females of child-bearing potential are not pregnant if they are to participate in such studies. See CPHS guidelines MRI in Research for discussion of screening requirements for female subjects (by age group) in studies involving the most commonly used such procedures in UC Berkeley research. Template biomedical assent and permission forms are also available for suggested language in this regard. Provisions for similar procedures/drugs not covered in these guidelines will be evaluated on a case-by-case basis during CPHS review.

5. ***Minors in Long-Term Studies***

Long-term research studies may involve subjects who are minors at the time of enrollment, but reach the age of majority while study procedures or follow-up are still ongoing. The CPHS will consider on a study-by-study basis whether obtaining new consent from such subjects is required. Usually, if there is continued interaction with subjects who were first enrolled as minors, re-consenting when a subject's legal status changes will be required. If the only continuing study procedures are follow-up activities such as review of records or analysis of biological specimens, the original consent may suffice. This will be determined on a case-by-case basis.

6. ***Research Involving Children in Educational Settings***

When planning studies involving children/minors in educational settings, investigators should consider the following issues (also see CPHS Guidelines on Child Assent and Parent Permission):

a. *Agreement/support from school official(s)*: While the CPHS no longer requires a letter of support for the research from officials at the school site(s), the protocol must include an affirmation that the investigator(s) and school officials are familiar with and will comply with all relevant regulations/laws, such as FERPA and PPRA (see below for details). Note that school officials and/or teachers may approve recruitment for a study, but they do not have authority to give permission for participation of individual minors in research—only a parent or guardian may do so.

b. *Parent permission*: Investigators have sometimes proposed obtaining "implied" or "passive consent" (permission) from parents of prospective subjects when they wish to carry out minimal risk research in a classroom or school setting (e.g., a child takes home information about participating in a study at school, and an absence of response from the parent is considered agreement). In fact, federal regulations do not recognize the concept of "passive consent."

If the investigator wishes to carry out research in such populations without *signed* permission, he/she must request a *waiver of documented consent/permission* from the CPHS/OPHS. For research without obtaining *any* parental permission, the investigator must obtain agreement from the school and request a *waiver of parent permission* (see CPHS Guidelines on Child Assent and Parent Permission). In either case, it is likely that an information sheet/letter to the parents will be required.

c. *Audio- or video-recording in the classroom*: If the investigator wishes to audio or video record in a classroom, special attention must be paid to issues of confidentiality, permission, and assent. If some

parents do not wish to have their child recorded, or the child himself/herself does not wish to be recorded, how will this be handled? Will investigators be able to audio- or video-record only certain (participating) individuals in a group setting? Can they delete or blur faces on video and/or delete or mask voices on audiotape? The investigator must describe in the protocol, and make clear in the permission/assent forms, all provisions made in this regard.

Research Media Records Release Form: As with any study, if the investigator wishes to retain audio or video recordings for future use, students and their parents must have the opportunity to give specific, usually separate, agreement for this. See Research Media Records Release Form for a sample release form, and see Instructions for Consent Form Reference to Media Records Release Form, which also apply to assent and permission forms.

d. *Offering alternative activities*: If the study will be conducted during school hours, an equivalent alternate activity, planned in advance with the teacher, should be available for students who do not wish to participate in the research.

e. *Additional regulation regarding educational research*: FERPA and PPRA are federal laws regarding privacy/access to student records and information, which apply to schools receiving funds from the US Department of Education (ED) and/or where the research is conducted under the ED.

- ***FERPA*** *(Family Educational Rights and Privacy Act)* is intended to protect the privacy of student education records. It gives parents rights with respect to their children's records (which transfer to the student when he/she turns 18). FERPA prevents schools from disclosing or allows schools to disclose these school records without written permission under certain specified conditions. (For additional information, see http://www2.ed.gov/policy/gen/guid/fpco/ferpa/index.html).

- ***PPRA*** *(Protection of Pupil Rights Amendment)*, an amendment to NCLB (No Child Left Behind), is intended to further protect the rights of students and parents by ensuring that schools make student surveys available for parents' inspection, and, if the research is funded by the US ED, that the researcher obtains written parental permission before students are allowed to participate in any survey, analysis, or evaluation that reveals information related to specified topics. (For additional details, see http://www2.ed.gov/policy/gen/guid/fpco/ppra/index.html, and for NCLB-related updates, http://www.fldoe.org/safeschools/pdf/ppra_recent_changes.pdf).

Note: Investigators who wish to obtain information from student records and/or conduct an ED-funded survey or evaluation should be aware of these laws, and should provide assurance to CPHS within the protocol that such activities will conform to the schools' implementation of either/both laws as applicable.