

Guidance and Procedure: Research Involving Children and Minors (updated October 19, 2020)

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Overview

When planning a study that will involve children, the principal investigator (PI) should first consider five main issues:

- What is the **rationale for including children**? What unique outcomes, benefits, and risks will come from studying children? Does the study address a condition that particularly affects children?
- What is the study **risk level** for the participants? What are the categories of risks permitted by the regulations?
- Does this research provide a **direct benefit** to the participating children?
- How are study procedures different from **standard of care** for the subjects?
- What are the **assent requirements** for the child or adolescent and what permissions will be needed from the parents?

Special considerations apply when research involves subjects who are minors (in California, under 18 years of age). Such research is important to obtain accurate data and develop optimal therapies for children. At the same time, children are inherently more vulnerable than adults, and require a higher level of protection.

Federal regulations for research with adult subjects [Title 45-Code of Federal Regulations \(CFR\)-Part 46](#) serve as a starting point. Additional special considerations for children are outlined in [45 CFR 46, Subpart D](#) and [21 CFR 50](#) for Food and Drug Association (FDA)-regulated research and interpreted by UCLA's Institutional Review Board (IRB) as described below. California laws also apply to research involving children conducted in the State of California (see below). There may be additional laws or requirements for research involving children being conducted in other states or internationally.

The purpose of these guidelines is to assist investigators in applying for UCLA IRB approval to conduct studies involving children. See [OHRPP Guidance and Procedures: Child Assent and Permission by Parents or Guardians](#) for detailed information on this important related topic.

Defining “Children” and “Minors”

These guidelines use the following terminology:

- **“Children”** are people who have not reached the legal age to consent for treatment or procedures involved in the research. In California, the legal age is usually 18, but there are important exceptions, explained below. Researchers working in other states or countries must learn about local laws governing the legal age of consent for the treatment or procedures involved in the research.
- **“Minors”** are people under 18 years of age. Because in California some people under 18 years of age can consent for themselves to some research procedures, not all “minors” meet the federal criteria for being “children.”

Both common speech and California law use the terms “children” and “minors” inconsistently. In the great majority of cases, people who are “minors” under California law are also “children” under the federal regulations. Nevertheless, occasionally the difference is significant. These guidelines attempt to use the terms consistently as described above.

Federal Regulations Regarding “Children:” Federal regulations (both 45 CFR 46 and 21 CFR 50) state, “‘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.”

In other words, who qualifies as a “child” depends on local laws for consent (and not necessarily on local definitions of the word “child”). In California, 18 is the usual age at which people can consent to treatments or procedures, but there are important exceptions, such as when seeking medical care related to the prevention or treatment of pregnancy (but see below for limitations).

IMPORTANT NOTE: 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 (for example, the requirement for permission of one or two parents in addition to assent from the “child.”)

California Law and “Minors:” For research conducted in California, people considered minors or children by California law usually also are considered “children” in the applicable Federal regulations. California law uses both terms to refer to people who are under 18 years of age. For example, California Family Code 6500 defines “minor” as “an individual who is under 18 years of age” and California Family Code 3402 says a “child” is “an individual who has not attained 18 years of age.” For clarity, these guidelines use “child” for people who meet the federal definition and “minor” for those who are under 18.

“Minors” Who Are Not “Children:” In California certain people under 18 years of age are legally able to consent for treatments or procedures involved in research. In the terms used in these guidelines, they are minors but not children.

For example, California Family Code 6925 says, “A minor may consent to medical care related to the prevention or treatment of pregnancy.” The minors in a study involving prevention of pregnancy are of legal age to consent to the treatment or procedures involved in the study. Therefore they are not “children” as defined in federal regulations. They can sign their own consent form as if they were adults, and parental permission is not required.

Other examples of people under 18 able to consent to treatment or procedures in California include *self-sufficient minors* and *emancipated minors*. Additional information is provided in [OHRPP Guidance: Child Assent and Permission by Parents or Guardians](#).

Other Definitions

The following definitions are based on U.S. Department of Health and Human Services (DHHS) regulations at 45 CFR 46.402, FDA regulations at 21 CFR 50.3, and California law.

- **Assent** is the term used for a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- **Adolescent** is the term used by California law to refer to a minor (see also definition of "minor" above).
- **Guardian** is an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. The FDA definition continues with the phrase "when general medical care includes participation in research." For research conducted outside California, the process described in the [Research Conducted Outside of California](#) section of this guidance will be used to decide which individuals in the local jurisdiction meet the DHHS and FDA definition of "guardian."

In California, a guardian may be a parent, a legally appointed guardian, a guardian *ad litem* as appointed by a court (this is an individual who may have no relationship to the minor who is appointed by the court to protect and represent the interests of the minor before the court), or others as consistent with an order of a court having jurisdiction over the minor. For wards of a court, usually an order from the judge is required in addition to permission from the person charged with care of the child.

- **Parent** is a child's biological or adoptive parent.
- **Permission** is the agreement of parent(s) or guardian(s) to allow the participation of their child or ward in research.
- **Wards (specifically defined only by the FDA)** are children who are placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

Rationale for Inclusion of Children in Research

As in any human research application, the choice of subject population must be explained. The investigator should analyze what is unique to children in formulating this rationale, as well as in assessing the risks and benefits of the study (see below).

Both the researcher and the IRB must consider the benefits, risks, and discomforts inherent in the proposed research and assess their justification in light of the expected benefits to the children or to society as a whole. In calculating the degree of risk and benefit, both the researcher and the IRB should weigh the circumstances of the subjects, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

Examples of appropriate rationales for inclusion of children in research

Note that many other examples could be listed.

The research holds out the prospect of benefit to children and involves:

- A condition uniquely affecting/manifesting in children (e.g., pediatric cancer; SLE [systemic lupus erythematosus]).
- A condition affecting both adults and children, where adult studies have been done but child specific data is still needed.

- An area of psychology or sociology specifically related to children (e.g., adolescent depression, childhood abuse).
- A pediatric condition linked to a different adult condition, so data could inform treatment of adult condition (e.g., Down’s syndrome/Alzheimer’s disease).

Permitted Categories of Research Involving Children

Assessing Risk: Research vs. Standard of Care

Federal regulations classify permissible research involving children into four categories, based on degree of risk and type of prospective benefit. These categories are described in relation to “minimal risk.”

- **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 21 CFR 50.3].
- **Greater than minimal risk** is a term used in defining Category 2 [45 CFR 46.405 21 CFR 50.52] and Category 3 [45 CFR 46.406 21 CFR 50.53]. The regulations do not provide any further definition of this term (except for specifying “a minor increase over minimal risk” in regards to Category 3 only). Thus, the protocol should clearly describe the study risks so that the CHR can determine into which category the study fits.

IMPORTANT NOTE: When assessing risk/benefit level, keep in mind that what constitutes “daily life” or a “routine test” may not be constant over childhood, among children of the same age, or before and after the occurrence of a disease or condition.

- **Standard of Care:** A vital part of the risk/benefit assessment is *clarifying what would be standard of care for the subject group(s) and how the research procedures differ from that standard of care.* The application should clearly convey this distinction. The consent/assent forms need only discuss in detail procedures (and their risks) that are being done specifically for purposes of the study.

Permitted Categories for Research with Children

The federal regulations require IRBs to classify research involving children into **one of four categories** and to document their discussions of the risks and benefits of the research study. Investigators conducting research involving children should familiarize themselves with the four categories of research involving children that may be approved by IRBs, based on degree of risk and benefit to individual subjects, are as follows:

45 CFR 46.404, 21 CFR 50.51: Research not involving greater than minimal risk.

The IRB may approve the research if it finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of one parent/legal guardian.

Example: A study involving one venipuncture (no more than the lesser of 50 ml or 3 ml/kg in an 8 week period) in healthy 10-year-old subjects.

45 CFR 46.405, 21 CFR 50.52: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

The IRB may approve the research if it finds and documents that:

- The risk is justified by the anticipated benefit to the subjects;
- 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
- Adequate provisions are made for soliciting the assent of the children and permission of one parent/legal guardian.

Example: A Phase II study using an experimental chemotherapeutic regimen for children with malignant brain tumors for whom standard therapy has failed.

45 CFR 46.406, 21 CFR 50.53: 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

The IRB may approve the research if it finds and documents that:

- The risk represents a minor increase over minimal risk;
- 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;
- 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
- Adequate provisions are made for soliciting assent of the children and permission of both parents/legal guardians.

Example: A study testing new biomarkers of disease progression that involves 2 extra samples of cerebrospinal fluid over a year of therapy (beyond the 5-6 that would be done as part of the child's routine care.)

45 CFR 46.407, 21 CFR 50.54: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

The research may only proceed if the Secretary of the Department of Health and Human Services (DHHS) (or, if the research is subject to FDA regulations, the Commissioner of Food and Drugs), after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of the above noted categories of risk 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;
- Adequate provisions are made for soliciting the assent of children and the permission of both parents/legal guardians as set forth in [45 CFR 46.408](#) (or [21 CFR 50.55](#)).

Example: A study examining sleep mechanisms in children to better understand sleep-related diseases. Involves 13- to 17-year-old adolescents undergoing 3 hospital visits for IV infusion of acetate and glucose followed by MRI, in normal and sleep-deprived groups.

California Health & Safety Code Section 111530(b), permits use of experimental drugs in minors only when the experimental drug is related to maintaining or improving the health of the subject or related to obtaining information about a pathological condition of the subject.

The FDA expects that component analysis will be used when determining the child risk category for a clinical investigation. This means that each research intervention or procedure will be evaluated separately to determine whether it does or does not hold out the prospect of direct benefit to the enrolled child.

NOTE: [FDA](#) does not consider the administration of a placebo to a child to offer a prospect of direct benefit to the recipient.

Wards of the State

[45 CFR 46.409](#) (and [21 CFR 50.56](#) for FDA-regulated research): Children who are wards of the state or any other agency, institution, or entity can be included in research posing greater than minimal risk with no prospect of direct benefit to subjects or requiring the approval of the HHS Secretary or FDA Commissioner *only* if the IRB finds and documents that such research is:

- Related to their status as wards; or
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.
 - If the IRB makes either of the above determinations, the IRB must also 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.

Investigators are responsible for awareness of and compliance with any relevant requirements of the competent court, agency, institution or entity of which the child is a ward.

Special Recruitment Considerations

Minimizing Pressure to Participate

When children are asked to do something by parents, doctors, teachers, or other adult authorities, they often feel implicit pressure to agree. Similar issues with social or peer pressure (e.g., for studies in educational settings) may also arise in recruiting children to participate in research.

APPLICATION NOTE: Investigators should describe in the Recruitment section of the webIRB application how they plan to minimize implicit pressure to participate. As with all consent and assent forms, the freedom to decline participation should be made clear.

Miscellaneous Arrangements

In designing studies involving children, investigators should consider any special arrangements for participation, such as scheduling, parking, and food, and discuss them with parents if appropriate. Though such information is not required, it could be helpful to parents in deciding about or planning for study participation.

Examples of special study arrangements to consider:

- If the subject is to receive a series of procedures or tests, can these be coordinated with school and/or work schedules?
- Are there siblings who will need child care or other provisions made?
- What about transportation and/or parking permits for the facility where the research is being conducted?
- Will participants or their family members need snacks or meals during the study?

Payment and Reimbursement

- **Ethics and regulations:** Ethical considerations regarding payment of subjects who participate in studies become even more complex when the research involves children. The regulations offer no specific guidance in this regard; IRBs have varying perspectives and policies. The UCLA IRBs neither encourage nor prohibit payment of children in research studies, but consider such proposals on a case-by-case basis.
- **General guidelines:** When evaluating this issue, the researcher should and the IRB will consider whether the payment, if any, is appropriate for the child. Factors such as age, health, socioeconomic and cultural backgrounds of the subjects need to be carefully considered to ensure that proposed payment does not constitute undue inducement to participate. See [OHRPP Guidance: Payment for Participation in Research](#).
- **Amounts and recipients of payment:** Investigators should propose payment or an equivalent token of appreciation that would be appropriate for children in relation to the tasks and/or procedures they will be asked to complete. In most cases, payment for study participation should be made directly to the subject or to both child and parent(s) at the same time, rather than to the parent(s) alone.
- **Reimbursement:** The IRB considers reimbursement separately from payment, and recommends that study participants or their families be reimbursed for expenses related to research (e.g., parking, travel, meals) whenever possible. If participants need to keep copies of receipts to be reimbursed, they should be told this in the consent form.

Requirements for Child Assent and Permission by Parents or Guardians

This important topic is discussed in separate guidance. See [OHRPP Guidance for Child Assent and Permission by Parents or Guardians](#).

Difficult Issues

Discovery and Disclosure 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, cancer, 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](#) for information as to whether this is applicable for a particular study).

- As with all UCLA consent forms, complete confidentiality should never be promised. See [UCLA consent templates](#) 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 ([California Penal Code 11164-11174.4](#)). Even if the mandated reporter status is not clear, the investigator 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 forms must indicate how discovery of such information will be handled.
- 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 or an Assistant Director of the UCLA OHRPP, who may refer the question to UC Legal Counsel.
- See also [OHRPP Guidance on Reporting of Suspected Abuse or Neglect of Children, Elderly Individuals, and Dependent Adults](#).

Enrolling Children in Long-Term Studies

Long-term research studies may involve subjects who are children at the time of enrollment but who reach the age of consenting for themselves (in California, usually 18 years old) while study procedures or follow-up are still ongoing. The researcher should and the IRB will consider on a study-by-study basis whether obtaining new consent from such subjects is required. See [OHRPP Guidance: Child Assent and Permission by Parents and Guardians](#).

Research Conducted Outside of California

UCLA researchers enrolling research participants in other states or countries should:

- ***Comply with local law regarding consent requirements.*** In all cases, if the prospective subjects *cannot* legally consent for the treatments or procedures involved in the study because they are too young, they are considered “children” by federal regulations. If they *can* consent for the treatments or procedures, they are *not* “children” by federal regulations. Researchers working in other states or countries should consult with their local collaborators about applicable laws and regulations.
- ***Research local requirements regarding who qualifies as a “child” or “guardian”*** under the federal definitions provided below, and whether local requirements provide any other unique protections to children. *Please note:* Another jurisdiction’s definition of “guardian” in and of itself does not mean a “guardian” under the federal definition. The federal definition hinges on whoever may, under local requirements, provide consent on behalf of the child for general medical care.
- ***Describe the research team’s knowledge of local requirements*** and how appropriate consent and assent will be obtained in the IRB application.

The IRB will evaluate whether the investigator’s plans demonstrate knowledge of local requirements. OHRPP staff will confirm information provided by the investigator, with the assistance of University Counsel as needed.

Additional IRB Responsibilities

When reviewing research involving children and adolescents, the IRB has additional responsibilities it must meet:

- **Include Appropriate IRB Expertise When Reviewing Research Involving Children:** An IRB considering a protocol involving children as participants is required to:
 - Assess its needs for pediatric expertise among the IRB voting membership to assure that it possesses the professional competence necessary to review the specific research activities; and
 - Consider inclusion of one or more individuals who are knowledgeable about and experienced in working with children. To fulfill this requirement, the IRB may invite nonvoting individuals to assist in the review of issues which require expertise beyond, or in addition to, that available among voting IRB members.
- **Apply Federal Criteria for Special Protections for Research Involving Children:** In addition to applying the federal criteria for approval of research involving human subjects, the IRB will also assess whether proposed research involving minors constitutes activities covered under 45 CFR 46 Subpart D, 21 CFR 50 for FDA-regulated research, and/or applicable California law and if so ensure that special protections are appropriately applied.
- **Assess whether Participants are Minors or Children**

If the proposed research activities include interventions with minors, such as pregnancy testing, the IRB will assess whether the minor is a child under applicable federal regulations and State law for the purpose of that specific intervention.

- If the subject is a minor as defined by State law and unable to legally participate in the procedure without parent-guardian permission, the IRB will apply all of the applicable protections at 45 CFR 46 (Subpart D).
- If the subject is *not* a child as defined at 45 CFR 46.402 and by California law, the IRB will determine whether additional protections at Subpart D should be applied in order to ensure the research demonstrates respect for the dignity of the subject as well as minimize risks and maximize benefits, e.g., including an appropriate alternative mechanism for protecting the children, such as a subject advocate, as outlined in 45 CFR 46.408(c).

Research Involving Children in Education Settings

When planning studies involving children in educational settings, investigators should consider a number of issues. See OHRPP Guidance document on [Student Subject Pools](#).

References

DHHS Regulations and Guidance

- [45 CFR 46, Subpart D: Additional Protections for Children Involved as Subjects in Research](#)
- [45 CFR 46.408\(c\): Requirements for Permission by Parents or Guardians and For Assent by Children](#)
- [OHRP \(formerly OPRR\), *Protecting Human Research Subjects Guidebook \(1993\) Chapter 6, Section C, "Children and Minors."*](#)
- [National Institutes of Health \(NIH\) Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects](#)

- [2005 Secretary's Advisory Committee on Human Research Protections Recommendations and Discussion for Research Involving Children](#)
- [FAQs on Research with Children](#)

FDA Regulations and Guidance

- [21 CFR 50, Subpart D: Additional Safeguards for Children in Clinical Investigations](#)
- [FDA Guidance for Clinical Investigators, Institutional Review Boards and Sponsors: Process for Handling Referrals to FDA under 21 CFR 50.54](#) – December 2006.
- [U.S. Food and Drug Administration \(FDA\): Guidance for Institutional Review Boards and Clinical Investigators](#) ; [Office of Pediatric Therapeutics](#); [Pediatric Advisory Committee \(PAC\)](#)
- [Institute of Medicine, The Ethical Conduct of Clinical Research Involving Children \(2004\)](#)

EPA Regulations

- [40 CFR 26, EPA Policy for Protection of Subjects in Human Research Conducted or Supported by EPA](#)

UCLA OHRPP

- [Child Assent and Permission by Parents or Guardians](#)
- [Research Involving Students and/or Conducted in Educational Settings](#)
- [Students and Employees](#)
- [Student Subject Pools](#)
- [Reporting Suspected Abuse of Children, Elderly Individuals and Others](#)
- [Certificates of Confidentiality](#)
- [EPA checklist](#)

Journal Articles:

- Sugarman J. Determining the appropriateness of including children in clinical research. JAMA 2004; 291(4):494-496.
- Kodish E, Eder M, Noo R, Ruccione K, Lange B, Angiolillo A, Pentz R, Zyzanski S, Siminoff L, Drotar D. Communication of randomization in childhood leukemia trials. JAMA 2004; 291(4): 470-475.
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Change log:

10/19/2020: Added information on component analysis; updated links.