



Human Subject Protection Program
Investigator Guidance
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Research Involving Children

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Introduction

Most of the research studies and clinical trials at CHLA involve children as research participants. This guidance document provides information about obtaining and documenting permission (consent) from parent(s)/guardian(s) and assent from children to participate in research.

Definitions

- **Assent** means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- **Permission** means the agreement of parent(s)/guardian(s) to the participation of their child or ward in research.

- **Parent** means a child's biological or adoptive parent.
- **Guardian** means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. The role of a guardian in the context of research involving a child who is a ward is to provide permission, in lieu of a child's biological or adoptive parents, for the ward to participate in the research. (A guardian is the equivalent of a legally authorized individual acting on behalf of an incapacitated adult.)

Who is Considered to be a Child?

- 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 where the research will be conducted.
- In the state of California, all individuals under the age of 18 years are children with exceptions such as emancipated and self-sufficient minors and in certain treatment circumstances. Refer to *HRP-013 SOP - Legally Authorized Representatives, Children and Guardians* for more details.

Obtaining Child Assent

While children do not have the legal capacity to “consent” to participate in research, they should be involved in the consent process if they are able to “assent” by having a study explained to them and/or by reading a simple form about the study, and then giving their verbal choice about whether they want to participate. Older children may also be able to provide a written assent.

CHLA requires assent to be obtained (not necessarily documented) from children 7 years of age or older, per CA law. Assent is not required from children who do not have the capacity to assent.

- In determining whether children are capable of assenting, the ages, maturity, and psychological state of the children involved should be taken into account. This determination may be made for all children and adolescents to be involved in research under a particular protocol, or for each child, as appropriate.
- An assent process that takes into account the child's experience and level of understanding, assures an element of cooperation and a feeling of inclusion on the part of the child, and also illustrates the investigator's respect for the rights and dignity of the child in the context of research.
- Out of respect for children as developing persons, they should be provided with essential information and asked whether or not they wish to participate in the research, particularly if the research: (a) does not involve interventions likely to benefit them; and (b) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

- Refer to the CHLA IRB or external Reviewing IRB approval letter for details about when children must provide verbal or written assent to participation on research.

Documentation of Child Assent

- The IRB determines whether assent from a child needs to be documented, and the way it should be documented. Assent may be documented by the investigator on the permission (consent) form or on a separate assent form.
- The CHLA IRB prefers that the investigator document each child's assent on the permission (consent) form signed by their parent(s)/guardian(s). An external Reviewing IRB may decide to have assent documented by the investigator on a separate assent form.
- The abilities and needs of children vary widely and investigators should provide subjects in a format tailored to the child. A simplified assent form should be used that includes relevant information about the research so that a child can decide whether to participate. The CHLA simplified assent form template includes the signature of the child but is left optional.
- The CHLA IRB prefers the simplified assent form be used as a guide and that investigators focus on the **assent process** rather than on obtaining a signature for a form.

Obtaining Parental Permission (Consent)

- Adequate provisions must be made for soliciting the permission of each child's parent(s)/guardian(s).
- Children have neither the legal status nor the developmental capacity to understand many of the issues inherent in providing informed consent. Parent(s)/guardian(s) must provide their permission for a child's participation in research just as they provide permission for clinical care.
- Obtaining and documenting permission (consent) must follow the CHLA investigator guidance document, *Obtaining and Documenting Informed Consent and Assent*.

Additional Protections for Children

Federal regulations include additional protections for children involved as subjects in research and establish risk-benefit categories for research involving children. Only research that fits into one of the 3 categories (45 CFR 46.404, 45 CFR 46.405, and 45 CFR 46.406) may be approved by an IRB. A 4th category (45 CFR 46.407) requires the approval of the Secretary of the Department of Health and Human Services.

The IRB assigns a risk-benefit category to all research involving children as subjects. The risk category is listed in the IRB approval letter. The IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405. Where research is conducted under 45 CFR 46.406 or 45 CFR 46.407, permission must be obtained from both parents 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. This determination will also be included in the IRB approval letter.

Child Risk Category	Parental Permission (Consent) and Assent Requirements	Additional Information
<p>Category 1 (§46.404/50.51): Research not involving greater than minimal risk.</p>	<ul style="list-style-type: none"> ➤ Permission of a one parent/guardian may be deemed sufficient. ➤ Assent of the child (when applicable) is required. 	<ul style="list-style-type: none"> ➤ Definition of Minimal Risk: The probability and magnitude of harm or discomfort anticipated in the research that 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. ➤ Whose daily life? The daily life of the general population. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).
<p>Category 2 (§46.405/50.52): Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject.</p>	<ul style="list-style-type: none"> ➤ Permission of one parent/guardian may be deemed sufficient. ➤ Assent of the child (when applicable) is required. 	<p>Benefits¹:</p> <ul style="list-style-type: none"> ➤ Direct benefit to subjects: Defined as benefit arising from receiving the intervention being studied. ➤ Collateral benefit to subjects: Benefit arising from being a subject, even if one does not receive the experimental intervention (for example, a free physical exam and testing, free medical care and other extras, or the personal gratification of altruism)
<p>Category 3 (§46.406/50.53): Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but</p>	<ul style="list-style-type: none"> ➤ Permission of both parents/guardians is required. ➤ Assent of the child (when applicable) is required ➤ If one parent/guardian is not reasonably available, the consent of a single parent may suffice. 	<p>Benefit¹:</p> <ul style="list-style-type: none"> ➤ Aspirational benefit to subjects: Benefit to society and to future patients, which arises from the results of the study. ➤ If the research activity or a component of the research is purely for research purposes and is not for the participants direct benefit, the IRB can only approve the research if the

¹ Journal of Law, Medicine & Ethics: 2000; v28, vi, pg332

likely to yield generalizable knowledge about the subject's disorder or condition.	<ul style="list-style-type: none"> ➤ See section “Obtaining Signatures from Both Parents” below for more information. 	<p>risks are not more than a minor increase above Minimal Risk.</p> <ul style="list-style-type: none"> ➤ It is the investigator's responsibility to provide the IRB with as much information as possible about the probability and magnitude of all possible harms from the procedure or intervention.
Category 4 (§46.407/50.54): Research that is not Otherwise Approvable	<ul style="list-style-type: none"> ➤ Permission of both parents/guardians is required. ➤ Assent of the child (when applicable) is required ➤ If one parent/guardian is not reasonably available, the consent of a single parent may suffice. ➤ See section “Obtaining Signatures from Both Parents” below for more information. 	<ul style="list-style-type: none"> ➤ If the IRB determines that the research does not fit into Categories 1-3 above, then the only way for the research to proceed is if the Secretary of Health and Human Services determines that it meets the criteria this category. ➤ The Secretary requests the FDA's Pediatric Subcommittee to review the proposal and make a determination. ➤ The Pediatric Subcommittee could either find that the research fits into one of the other 3 categories, or that the research meets the requirements of §46.407 or that the research is not approvable.

Obtaining Signatures from Both Parents

Both parents’ signatures do not necessarily have to be obtained at the same time. The timing of consent signatures might involve a combination of in-person and remote consenting procedures. The consent conference and documenting permission (consent) must follow the CHLA investigator guidance document, *Obtaining and Documenting Informed Consent and Assent*.

- The investigator should create a consenting note to document why signatures were obtained on two separate dates or on two separate consent documents.
- Investigators are encouraged to consult the IRB in specific situations for guidance.
- If investigators foresee that obtaining consent remotely from the second parent may be necessary for a study, the consenting plan submitted for IRB review and approval should include how this would be accomplished.

What is “**not reasonably available**”?

- “Not reasonably available” does not mean that a parent is temporarily unavailable, unless there are specific circumstances where time is of the essence.
- “Not reasonably available“ does not apply to situations when a parent is at work, at home, traveling, not immediately available by electronic means, or living in another state or country, without more to justify the investigator’s inability to reach the parent and seek permission.

- Examples of situations when one may reasonably conclude that a parent is not reasonably available could include the following situations²:
 - The parent is incarcerated and not contactable.
 - The parent is on active military duty and not contactable.
 - The parent's whereabouts are unknown.
 - The parent is known but, upon inquiry, there is reason to believe that requesting permission would be inconsistent with the parent/child relationship, such as where there is reason to believe there is or has been domestic violence or other situations involving harm to the health or welfare of the child.

What if Parents Disagree?

- If there are two parents available to give permission but 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 risk categories, even if only one parent's signature is required. When both parents are involved in the decision, they must agree for the child to be enrolled.
- If a parent who was not involved or available for the original consent later becomes involved or available, the two parents must then agree.

Waiver of Child Assent

If either of the following are true, the IRB may determine that the assent of the children is not a necessary condition for the research:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- 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 IRB may also grant a waiver of assent if the criteria for a waiver of consent are met [Old Common Rule §46.116(d)/50.55(d) or New Common Rule §46.116(f)/50.55(d)].

Waiver of Permission (Consent)

The IRB may grant a waiver of permission (consent) if the criteria for a waiver of consent are met [Old Common Rule §46.116(d)/50.55(d) or New Common Rule §46.116(f)/50.55(d)] for research this is not FDA-regulated.

² 2018 recommendations from the Secretary's Advisory Committee on Human Research Protections

Some research may also be designed for conditions or for a subject population for which parent/guardian permission for inclusion in research is not a reasonable requirement to protect the subjects (e.g., neglected or abused children).

- **FDA-Regulated Studies:** The regulations lack the provision for waiver of permission (consent). This is because the FDA does not believe it oversees studies for which such a waiver is appropriate.
- **Non-FDA-Regulated Studies:** The IRB may waive permission per §46.408(c) 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.

Consent When Children Become Adults

Children who reach the age of majority (per CA Law, i.e., age 18, married, joined the armed forces, legal emancipation) during study participation must be re-consented as adults. The study team must describe the re-consenting process that will be followed in the IRB application or protocol. If the adult subject is incapable of providing consent, surrogate consent must be obtained per CA law. Refer to the CHLA investigator guidance document, *Consent from Adults that Require a Legally Authorized Representative*, for more details.