CHILDREN AS STUDY PARTICIPANTS IN RESEARCH	SOP 4.05.01

1. Purpose & Policy

The purpose of this SOP is to provide guidance for the review and conduct of research involving children as study participants in research at Caltech. IRB Policy Section 4.5.

2. General Information

Research involving individuals who are under the age of 18 years and therefore have not attained the California legal age for consent and who are not wards of the state or any other agency are "minors" or "children" in the context of human subjects research.

When children are included in human subjects research, investigators must ensure that additional safeguards are in place to protect their rights and welfare. Children are considered a vulnerable population because they may have limited capacity to fully understand research procedures, risks, and potential benefits. As a result, research involving children requires careful review by the IRB to ensure that the study complies with applicable federal and state regulations, ethical principles, and institutional policies.

Consistent with the ethical principles outlined in the Belmont Report, the IRB is responsible for ensuring that selection of children as research participants is equitable, that possible benefits outweigh risks of harm, and that benefits are maximized and risks are minimized. Because children cannot legally provide informed consent, research involving children generally requires parental or guardian permission as well as the assent of the child, when the child is capable of providing assent. The IRB must determine whether adequate provisions are made for obtaining parental permission and child assent in accordance with federal and state regulations. In reviewing such research, the IRB applies the requirements outlined in 45 CFR 46, Subpart D: Additional Protections for Children Involved as Subjects in Research, and when applicable, 21 CFR 50 for FDA-regulated research. The IRB also considers applicable state and local laws. Investigators must also comply with Caltech policies regarding interactions with minors, including requirements outlined in the Staff Personnel Memoranda on Minors (PM 9-1) and abide by Caltech's Standards for Interacting with Minors. Depending on the nature of the research activities, investigators and study personnel may be

required to complete mandatory reporter training, background checks, or other institutional requirements prior to interacting with minors in a research setting.

Definitions:

Children: 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. (45 CFR 46.402(a)). In California, individuals under the age of 18 are generally considered children and therefore cannot legally provide informed consent to participate in research or medical treatments unless specific legal exceptions apply. If the research will be conducted outside of California, please contact the IRB for guidance.

Assent: A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (45 CFR 46.402(b)). Assent should be obtained in a manner appropriate to the child's age, maturity, and psychological state.

Permission: The agreement of parent(s) or guardian(s) to the participation of their child or ward in research. (45 CFR 46.402(c)). Permission serves as the equivalent of informed consent for children who are not legally able to provide consent themselves. Depending on the level of risk and potential benefit associated with the research, permission from one parent or both parents may be required under federal regulations. (45 CFR 46.408).

Parent: A child's biological or adoptive parent. (45 CFR 46.402(d))

Guardian: An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care or participation in research.

Ward: A child who is placed under the legal custody of the state or another institution, agency, or entity, consistent with applicable federal, state, or local law (defined by the FDA at 21 CFR 503).

3. Training Requirements

In addition to the normally required and specific training for all human subjects research, investigators who recruit child participants or conduct research using data collected from child participants must complete the applicable CITI course: CITI - Vulnerable Subjects - Research

Involving Children – BIO or Research with Children – SBE, depending on whether the study is Biomedical or Social & Behavioral.

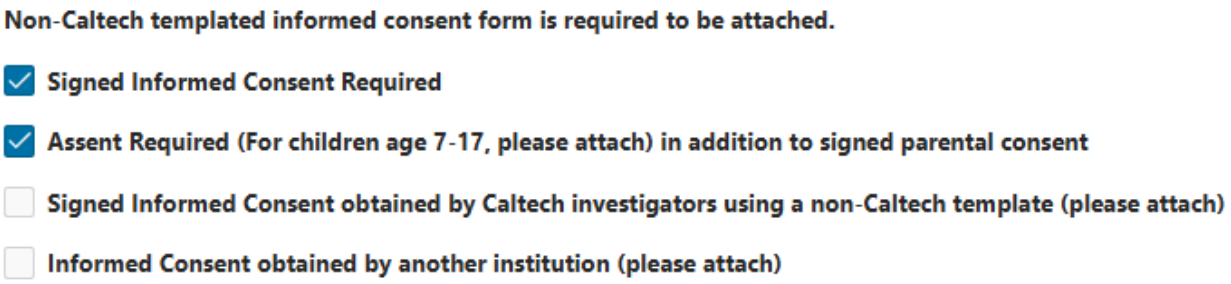
4. Procedure

A. Determination that Research Involves Children

In California, individuals under the age of 18 are generally considered minors and cannot legally provide informed consent to participate in research or medical treatments unless specific legal exceptions apply. Investigators must take reasonable steps to verify whether a participant is a minor or not. If age cannot be adequately verified, investigators must treat the participant as a potential minor and follow the applicable protocol for research involving children.

If children will be involved as research study participants, investigators must specify the age range of the child study participants and document their age-verification methodology in the Study Participation Selection section of the IRB protocol application.

If children age 7-17 will be involved in the study, the Assent Required box must be checked in the Informed Consent section of the IRB protocol application. See Assent Form Template below for assent and parental consent information and instructions.



B. Determination of Exemption Eligibility

The IRB will determine whether the proposed research involving children qualifies under exempt status under the categories described in 45 CFR 46.104 and section 6.3 of the Caltech IRB Policy.

Under these regulations, research involving children may be exempt from IRB review under the following circumstances:

- Educational Tests: Research involving educational tests may be exempt if the information collected cannot readily identify the participants and disclosure of responses would not reasonably place participants at risk of harm.
- Observation of Public Behavior: Research involving the observation of public behavior may qualify for exemption only if the investigator does not participate in the activities being observed.

Research involving surveys or interviews with children does not qualify for Exempt Category 2 under 46 CFR 46.104(d). Additionally, Exempt Category 3 (Benign Behavioral Interventions) are not applicable to research involving children. If research involving children does not qualify for exemption, the IRB must review the research according to the regulatory categories for research involving children under 45 CFR 46 Subpart D.

C. Determination Under 45 CFR 46 Subpart D

For research that is not exempt, the IRB must determine which regulatory category applies based on the level of risk and potential benefit to child study participants. Federal regulations permit IRB approval of research involving children only if the research falls into one of the following categories:

1. Research involving no greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)

   Assent from the child (when in the judgment of the IRB the child is capable of providing consent) and consent of at least one parent or guardian is required.

2. Research involving greater than minimal risk but presenting the prospect of direct benefit to individual study participants (45 CFR 46.405, 21 CFR 50.52)

   The risk must be justified by the anticipated benefit to the study participant, and the risk-benefit relationship must be at least as favorable to the study participant as that seen with available alternative approaches. Assent from the child (when in the judgment of the IRB the

child is capable of providing consent) and consent of at least one parent or guardian is required.

3. Research involving greater than minimal risk and no prospect of direct benefit to the individual participant but likely to yield generalizable knowledge about the participant's disorder or condition (45 CFR 46.406, 21 CFR 50.53)

   The risks associated with the research must be no more than a 'minor increase' over minimal risk, the risks must be reasonably commensurate with those inherent in the minor's actual or expected medical condition, and the research must be likely to yield generalizable knowledge of vital importance about the minor's disease or condition. Assent from the minor (when in the judgment of the IRB the child is capable of providing consent) and consent of both parents is required, unless a guardian has been lawfully appointed for the child (in which case the guardian's consent is required), or 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 minor.

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

   Such research requires expert consultation, an opportunity for public review and comment, and a determination by the U.S. Secretary of Health and Human Services before approval. Such studies normally cannot be conducted on campus or at JPL.

D. Parent Permission and Assent Requirements

Like the informed consent process, the assent process is intended to be an ongoing, interactive conversation between the research team, the child, and the child's parent(s) or guardian. The purpose of this process is not simply to get the child and parent(s)/guardian to assent to the research. It is to ensure that they understand the research and what it means to participate.

Because children cannot legally provide informed consent to participate in research, the participation of children generally requires both parental or guardian permission and the assent

of the child, when the child is capable of providing assent. The assent process should be an interactive communication between investigators and the child/parent(s)/guardian, designed to ensure that they understand the nature of the research, what participation involves and that participation is voluntary.

The IRB must determine whether the researchers have adequate provisions to solicit assent from child participants (when the children are capable of providing it), and the researchers must inform the IRB how the affirmative assent of such child participants will be documented (e.g., by signature on an assent form, through documentation by the researchers, or by other means). Unless there is a good reason not to collect the assent of minor participants, assent is required to be collected for all child participants who are seven (7) years old or older. For such children, the IRB recommends that researchers document the child's willingness to participate using a signed assent document if possible. Researchers must evaluate a child's capacity to assent on an individual basis. Although a formal assent process is not required for use with children less than 7 years old, each child should still be given a simple verbal explanation of what will happen to him or her, or what he or she will be asked to do, unless the child is not old enough to be consulted about participating in research.

When, in the judgment of the IRB, some or all of the minor participants are not capable of providing assent (taking into account the age, maturity, and psychological state of the participants), the IRB may approve research where the assent of some or all of the participants is not required. If the IRB determines that it is unreasonable to obtain parental consent for the participant population (e.g., in the case of neglected or abused minors), it may waive the consent requirements provided an appropriate mechanism for protecting the minors who will participate in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. Except when emergency medical care is required and in limited other circumstances, waiver of the consent requirement normally necessitates a finding by the IRB that the research involves no more than minimal risk to the participants, that the research could not practicably be carried out without the waiver, and that the waiver will not adversely affect the rights and welfare of the participants.

Parental or guardian permission must be obtained in accordance with the applicable Subpart D risk category, as outlined in section C (1-4) above and in Figure 1 below.

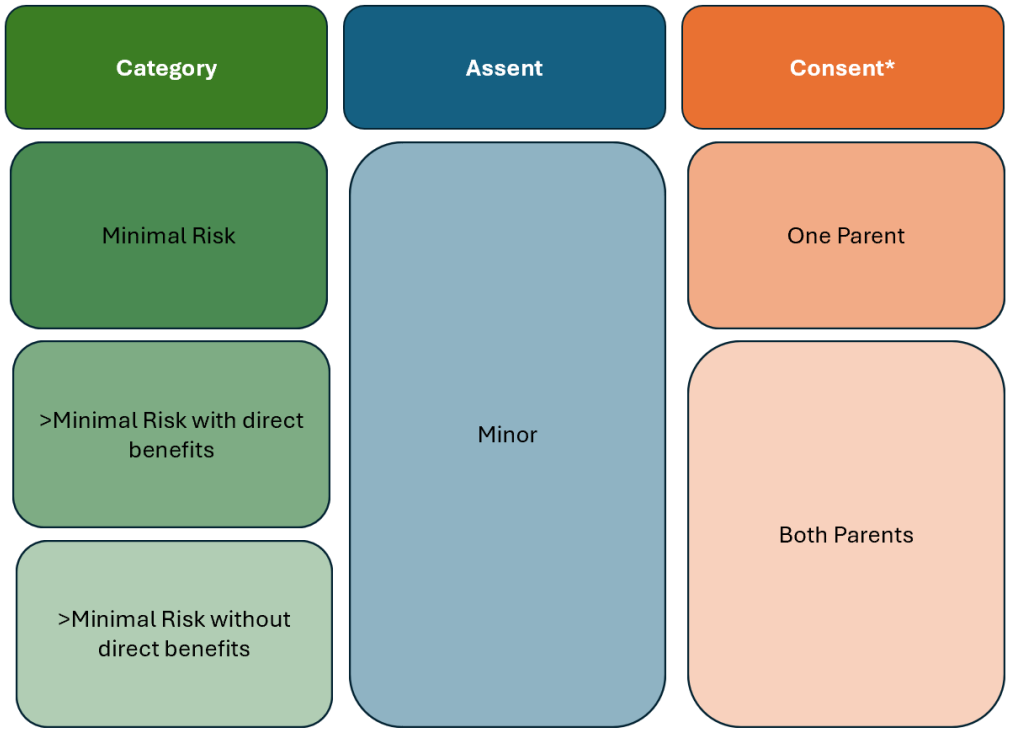


Figure 1

*With certain exceptions, for example both parents may not be required to consent when one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the child. In limited circumstances, the IRB may determine parental consent is unreasonable for the subject population, for example, in studies of neglected or abused children.

Research is generally not suitable for a consent waiver if the research involves:

- Parental political affiliations or beliefs;
- Mental or psychological problems;
- Sexual behavior or attitudes;
- Illegal, antisocial, or self-incriminating behavior;
- Appraisals of other individuals with whom the child has a familial relationship;

- Relationships that are legally recognized as privileged (e.g., with lawyers, doctors, or clergy); or
- Religious affiliations or beliefs.

E. Additional Protections for Wards of the State

Children who are wards of the state or any other agency, institution, or entity may be included in research only under specific conditions that are described in 45 CFR 46.409. Research involving wards may be approved only if:

1. The research is related to the ward's status as a ward, or
2. The research is conducted in schools, camps, hospitals, institutions or similar settings in which the majority of the participants are not wards.

When wards are included in the research, the IRB must require the appointment of an 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. That person must act in the best interest of the child for the duration of the child's participation in the research and be independent of the research, study investigators and the guardian organization.

F. Special Circumstances

If any the following circumstances are presented, please contact the IRB (irb@caltech.edu) for guidance:

1. The parents or guardian are unavailable.
2. The child has a guardian, and the research involves medical care.
3. The child is an emancipated minor or otherwise claims the right to consent as an adult (e.g., for care related to pregnancy, rape, sexual assault, alcohol abuse, or drug abuse).
4. The research will be conducted at a Department of Veterans Affairs facility.

G. Mandatory Reporting of Child Abuse and Neglect

Caltech has strict requirements for the reporting of child abuse and neglect. Researchers should be aware of Caltech's requirements and their obligations under California law. Please review Caltech's PM 9-1 Minors and particularly Caltech's policies on mandated reporters.

Steps To Make a Report:

1. Report to Caltech Security 626-395-5000,
2. Report to law enforcement or child protective services as soon as practicably possible by phone to LA County Child Protection Hotline (800) 540-4000 [or from out of state (213) 639-4500] or Pasadena Police Department 911 (for emergencies) or (626) 744-4501 (for non-emergencies), or to another local police department. Within 36 hours via a written Suspected Child Abuse Report.
3. Mandated Reporters must file a written Suspected Child Abuse Report (SCAR) within 36 hours of receiving information concerning the incident. The SCAR can be completed online at https://mandreptla.org.

ASSENT FORM TEMPLATE

1. Fill out the form with information specific to your study using language that is age appropriate for your study population.
2. Submit the revised template to the IRB for review and approval by attaching the document to your protocol application in IRB PAS.
3. When the IRB approves the study, the IRB-approved document must be used.

Most likely you will also need to create a Parental Permission form (see below).

Parental Permission Form:

The Parental Permission Form may be created by adding a cover page to the study's Informed Consent document indicating that the consent form will serve as the Parental Permission document for the study. The document should include a statement clarifying that "you" or "participant" refer to the parent's child. Investigators should follow the guidelines outlined in section to determine if one parent signature (for minimal risk research) or two parent signatures (for greater than minimal risk research) are required.

Using the Assent Form:

1. Introduce yourself to the child study participant and give them your name and inform them that you are a student/professor researcher at Caltech.
2. Review the Assent Form with the child study participant. Ask the child if they have any questions about the form or about their participation in the study. Spend as much time as necessary answering any questions and ensure all answers and explanations are delivered using age appropriate language.
3. Obtain child study participant signatures.
4. Review the Parental Permission with the parent(s). Answer any questions the parent(s) may have regarding the study, their child's participation, and/or the accompanying forms.
5. Obtain parental signature(s).

Assent for Participation in Research Activities
7-17 Years Old

Project Title: *PROJECT TITLE HERE*

Principal Investigator: *Principal Investigator Name*; Address: MC XX-XXX, California Institute of Technology, Pasadena, CA 91125; Phone: 626-395-XXXX; Email: XXXx@XXXXX

Approval Period: Pending IRB Decision

1. We are doing a research study. A research study is where scientists like me do research to find out more information about something. A research study is not medical treatment and I am not a medical doctor.

2. We are doing this research study because we are trying to learn more about *[Outline what the study is about in language that is both appropriate to the child's maturity and age]*

3. Why are we talking to you about this study: *[Describe who can participate and why the child is eligible]*

4. What will happen if you are in this study? *[Describe what will take place from the child's point of view in language that is both appropriate to the child's maturity and age]*

5. How long will the study take? *[Describe length of participate and duration, for example, 2 hours on two occasions, 2 weeks apart.]*

6. If you don't want to be in this study, you don't have to be*. [If applicable and appropriate, describe or let the child know the possible alternative(s).]* Even if your parents agree that you can be in the study, you can still decide not to be. If you agree to be part of the study, you can change your mind and may stop being in this study any time. Remember, being in this study is up to you and no one will be upset if you don't want to take part in this study or even if you change your mind later and want to stop. *[If applicable, indicate that sometimes it is not possible to stop the study all at once and why.]*

7. Sometimes bad things happen in research studies. Some of the bad things that could happen are: *[Describe any risks to the child that may result from participation in the research, include discomforts such as blood draws or laying still while imaging]*. Some of these things might happen to you or they might not. Or things might happen that we don't know about yet.

8. People may also have good things happen to them when they are in research studies. The good things may be *[Describe any benefits to the child from participation in the research]*.

9. *[Indicate if the child receives any payment for being in the research. If not, this item can be deleted. Explain that this a "thank you" for their time and effort]*

10. Who will know about your participation in this research study? Besides your parents, the researchers in this laboratory are the only ones that will know. We will keep your information confidential and secure in our laboratory. If we talk or write about this research or results from it, we will only discuss the results from the entire group that we are studying. We may share the information from this study with other researchers, but they will not be able to identify you.

11. Please talk this over with your parents and others you trust before you decide whether or not to take part in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

12. Please ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call [*Insert your telephone number*] or ask me questions at any time.

13. Please write and sign your name below if all of your questions have been answered and you agree to be a volunteer this research study.

_____
Name of Participant

_____ _____
Signature of Participant Date
(Please sign your name here)

_____
Name of Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date