Caltech

POLICY OF THE

CALTECH ADMINISTRATIVE COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS

INSTITUTIONAL REVIEW BOARD: IRB

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1. The Human Research Protection Program

1.1 MISSION

Research conducted at the California Institute of Technology (Caltech) encompasses a large range of fields that span all of Caltech's Divisions including the Jet Propulsion Laboratory (JPL). Research is conducted in several fields that, directly or indirectly, involve collecting, analyzing, and disseminating data from human subjects. A vital aspect of research at Caltech is the efficient and responsible conduct of such research. The overarching mission of the IRB is to ensure ethically responsible human subjects research at Caltech.

Caltech holds a Federal Wide Assurance (FWA), approved by the Office for Human Research Protections, U.S. Department of Health and Human Services, in which the Institute has agreed that federally funded human subjects research conducted at Caltech (including JPL) will be compliant with the Federal Policy for the Protection of Human Subjects (known as "The Common Rule" effective July 19, 2018[1] and the U.S. Department of Health and Human Services regulations for the Protection of Human Research Subjects: Title 45 of the Code of Federal Regulations, Part 46 (45 C.F.R. § 46). Caltech is also registered with the Food and Drug Administration (FDA) allowing Caltech investigators to conduct research studies with human subjects using experimental medical devices, drugs, and biologics (21 C.F.R. § 56).

The Caltech Administrative Committee for the Protection of Human Subjects functions as Caltech's Institutional Review Board (IRB) consistent with the Institute's FWA and seeks to ensure Caltech research on human subjects adheres to the Common Rule, 45 C.F.R. § 46, and 21 C.F.R. § 56. The IRB is also guided by the ethical principles regarding all research involving humans as subjects as set forth in the April 18, 1979, report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled: "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," commonly referred to as the Belmont Report.

The IRB approves, monitors, and provides advice on Caltech research involving human subjects to ensure the research is guided by uniform ethical principles that protect the rights and safety of human subjects. This protection is assured by consideration of three principles that are the basis of ethical research:

Respect for Persons: recognizing the personal dignity and autonomy of study participants and providing special protection of those participants with diminished autonomy. This is achieved through true free and informed

[1] and as applicable, the previous common rule effective July 14, 2009

consent. The Caltech IRB recognizes the need to explain a research study to prospective participants in language they can understand.

Beneficence: protecting study participants from harm by maximizing anticipated benefits and minimizing possible risks of harm. This is achieved through a risk-benefit analysis. The Caltech IRB recognizes that both risks and benefits are broad categories that need to be evaluated relative to everyday life.

Justice: ensuring that the benefits and burdens of research are distributed fairly. This is achieved by having no particular exclusions based on race, gender, age, or other characteristics unless these are scientifically justified. The Caltech IRB recognizes that participant sampling and generalizability are important aspects of research.

1.2 APPLICABILITY

This policy document applies to all research involving study participants conducted, supported, or otherwise subject to oversight by Caltech, regardless of the funding source, as well as teaching activities that involve human subjects.

In accordance with OHRP guidance, Caltech is engaged in human subjects research as defined by being involved in one or more of the following activities:

- Receiving an award through a grant, contract, or cooperative agreement directly from HHS or other federal agency for the non-exempt human subjects research (even when all human research activities are conducted by non-Caltech personnel)
- Intervening for research purposes with any study participant of the research by performing invasive or non-invasive procedures
- Intervening for research purposes with any study participant of the research by manipulating the environment
- Interacting for research purposes with any study participant of the research
- Obtaining the informed consent of study participants for the research
- Obtaining for research purposes identifiable private information or identifiable biological specimens from any source for the research.

1.3 DEFINITIONS

- Research

A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge[2].

- Human Subject (Participant)

  A living individual about whom an investigator (whether professional or student) conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimens or obtains, uses, studies, analyzes or generates identifiable private information[3] or identifiable biospecimens[4].

- Institutional Official (IO)

  The individual who is legally authorized to act for Caltech and obligates Caltech to the terms of the FWA.

- Principal Investigator (PI)

  An individual who submits and is responsible for an IRB protocol, limited to a Tenured or Tenure-track Professorial Faculty, a Research Professor, a JPL Investigator, an Associate Director or above, or a qualified External Affiliate.

- Investigator

  Anyone, other than the PI, who will conduct research under an approved IRB protocol. All protocols must be under the overall direction of a PI.

- The IRB

  "The IRB" may refer to quorum at a convened meeting of the IRB, or to the IRB Chair or subcommittee acting on behalf of the IRB where applicable.

1.4 AUTHORITY

The Administrative Committee on the Protection of Human Subjects fills the role of the Institutional Review Board (IRB) required by the US Public Health Services and the Food and Drug Administration. The IRB is charged with the responsibility of overseeing all human subjects research at Caltech, including the Jet Propulsion Laboratory. The IRB acts to protect the rights of study participants and promote the ethical and responsible treatment of participants in research.

[2] Research does not include: scholarly and journalistic activities that focus directly on the specific individual about whom information is being collected; nor public health surveillance activities; nor collection and analysis of information, biospecimens, or records for a criminal justice agency or for criminal investigations; nor authorized operational activities in support of intelligence, homeland security, defense or other national security missions.

[3] *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record). *Identifiable private information* is private information for which the identity of the participant is or may readily be ascertained by the investigator or associated with the information.

[4] An *identifiable biospecimen* is a biospecimen for which the identity of the participant is or may readily be ascertained by the investigator or associated with the biospecimen.

- The President appoints the IO and all IRB members.
- The committee charter, approved by the President, delineates the duties and responsibilities of each administrative committee. Amendments or revisions to a committee's charter will be recommended to the President by the IO.

The IRB is authorized to adopt its own rules of procedures, as long as such rules do not conflict with the provisions of the charter approved by the President.

No investigator may conduct human subjects research without approval of the IRB. The IRB has authority to grant approval for studies involving human study participants, to require modifications to a protocol to secure approval for studies involving human study participants, to suspend or terminate approval pursuant to these policies, or to grant an exemption pursuant to this policy. However, there may be occasions where ancillary approvals may be required in addition to IRB approval.

Studies involving study participants that have been approved by the IRB may be subject to further review by the Institute. Studies involving Caltech personnel as participants or using Caltech personnel data are subject to additional Institutional review. The IO may disapprove a protocol that the IRB has approved; however, they may not approve the research if it has not been approved by the IRB.

The United States Government has regulatory oversight over the Caltech IRB. The relevant agencies are the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), part of the U.S. Department of Health and Human Services. While the OHRP has authority over federally funded human subjects research conducted at Caltech, the FDA has authority over studies involving FDA-regulated products, including drugs, biologics, and devices.

The IRB Chair and Committee share authority over all IRB policies and procedures in collaboration with the IO. Any member of the IRB may at any time suggest revisions to the IRB Policy to the IRB Chair. It is also expected that the Policy will be amended in accordance with changes in federal regulations. The IRB Chair may revise the IRB Policy in consultation with the IO from time to time. Copies of proposed changes will be offered to the IRB via email and the IRB will be given one week for comment or objection; if there are no material objections, the proposed change will be considered accepted, and this will be ratified at the next meeting.

2. Composition of the IRB

2.1 IRB MEMBERSHIP IN GENERAL

The Caltech President appoints all members and the Committee Chair. The Committee composition meets all regulatory and institutional requirements. The Committee shall be composed of members with varying backgrounds to promote complete and adequate review of the research activities presented for consideration. The Committee shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of participants in human subjects research at the Institute.

In addition to possessing the professional competence necessary to review specific research activities, the Committee shall be constituted that the members have the ability to ascertain the acceptability of the proposed research in terms of institutional commitments, policies and regulations, applicable law, and standards of professional conduct and practice. Thus, the Committee shall include members representing a variety of professions.

Should the IRB regularly review research involving a vulnerable category of participants, consideration shall be given to including a member or non-member expert who is knowledgeable about and experienced in working with these participants. An IRB member may always request or suggest that an expert be included in protocol review.

To protect the privacy of research participants, promote open discussion at IRB meetings, to protect proprietary information (including intellectual property rights), and in some instances to meet the agreements with research sponsors, the protocols reviewed and the discussion at the IRB meetings should remain confidential as a general rule. However, other interests, such as the safety of study participants may outweigh the general rule of confidentiality. The meeting minutes should not attribute particular statements to individual IRB members, so as to promote free and critical discussion.

Members of the IRB receive training and continuing education to fulfill their duties as IRB members. This education includes training on Caltech's IRB Policy, the applicable federal regulations, and protocol review. Member education includes completion of the Collaborative Institutional Training Initiative (CITI) IRB Members training at least every five years. Continuing education may also include education in the fields of research done

at Caltech in order to review protocols more effectively, and education relating to the safety and privacy of study participants.

2.2 IRB MEMBERSHIP SPECIFICALLY

VOTING MEMBERS

The Caltech President will appoint the Chair and Vice-Chair. The Chair shall be responsible for calling and chairing meetings, receiving correspondence on behalf of the Committee, and speaking on behalf of the Committee. In the absence or unavailability of the Chair, the Vice-Chair or another faculty IRB member may assume all the Chair's responsibilities. On day-to-day and administrative matters, the Chair generally works closely with the IRB Administrator, and with the Institutional Official, as needed.

The voting members should include at least one of the following types of voting members: (1) a person whose primary focus is in a scientific field of work, (2) a person whose primary focus is in a non-scientific field of work, and (3) a person who is not otherwise affiliated with Caltech and who is not part of the immediate family of a person who is affiliated with Caltech. At Caltech, scientific members of the IRB shall include at least three faculty members from at least two different divisions and at least one active member of the research staff of JPL.

EX OFFICIO MEMBERS

The Senior Director of the Environmental, Health and Safety Office, the Senior Director for Research Administration or their delegate, and a representative from Caltech's Brain Imaging Center (CBIC) serve as ex officio members of the IRB. Ex officio members serve on the Committee as a result of the office or position that they hold. They stand outside any rotation of Committee membership as they hold the office designated in this paragraph. Ex officio members, or their designee, are voting members of the Committee.

The General Counsel and/or their designee shall serve as a Legal Advisor to the Committee for the purpose of providing legal advice to the Committee. The Legal Advisor participates, as appropriate, in the Committee's deliberations, but shall not serve as a member of the Committee.

The IO may attend and participate as an observer/consultant in the Committee's meetings but shall not serve as a member of the Committee.

ALTERNATES

The Committee may have up to three appointed alternate members substituting for voting, ex officio, or other members at a convened meeting. An alternate member may be assigned to substitute for several members but

may only substitute for one absent member at a time and must meet the member requirements for the person whom they are replacing (e.g., an alternate for the unaffiliated member must meet the requirements for an unaffiliated member).

Alternate members may regularly attend meetings but may only vote when substituting for a primary member. A designated alternate IRB member for a primary IRB member may substitute for the primary IRB member for an entire meeting or only a portion. Substitution during a meeting may occur when the primary member is absent for all or part of the meeting, or recused from review of certain research protocols because they have a conflicting interest with respect to those specific research protocols.

AD HOC ADVISORY MEMBERS AND GUESTS

The IRB may invite a nonmember advisor who is knowledgeable and/or experienced in working with vulnerable populations to the meetings ad hoc when protocols reviewed require additional expertise.

The IRB may also occasionally choose to invite investigators, students, or other relevant parties to attend meetings or part of a meeting as guests, with the understanding that confidentiality applies.

TERM

With the exception of ex officio members, IRB members shall be appointed for three-year terms and shall typically serve no more than two consecutive terms. However, the President, at their discretion, may appoint an individual to additional consecutive terms.

3. IRB Meetings

3.1 QUORUM

A majority of the members of the IRB must be present at meetings, including at least one member whose primary concerns are in nonscientific areas, and either the Chair, Vice-Chair or another faculty IRB member who will preside, to constitute a convened meeting of the IRB. Approval by a majority of those members present at the meeting is required to approve research, except when an expedited review procedure is used. Members may participate in a meeting by telephone or videoconference provided that (1) they have received all pertinent material prior to the meeting, and (2) they can actively and equally participate in the discussion of all protocols.

3.2 CONFLICTS OF INTEREST

From time to time, an IRB member will have a conflicting interest with a protocol. An IRB member will always have a professional conflict of interest in reviewing their own protocol. Other professional, financial, or personal conflicts of interest may arise as well. An IRB member with any conflicting interest should identify themselves as having a conflicting interest in a particular protocol, though the nature of the conflict need not be disclosed to the IRB.

No member may participate in the initial or continuing review of any study in which they have a conflicting interest, except to provide information requested by the IRB. The conflicted member should leave the meeting while the study is being discussed, except when the member is requested by the IRB to remain present to provide information. The presence or absence of the conflicted member should be reflected in the meeting minutes.

3.3 FREQUENCY

The IRB shall meet regularly to review and approve, require modification to, or disapprove all human subjects research performed at Caltech. The Caltech IRB meets approximately six times annually. Reviews that do not require Full Committee Review (e.g., exempt and expedited new protocols, as well as many annual renewals of protocols) are conducted by the IRB Chair (or Vice-Chair) and/or another IRB member(s) as needed on an ad hoc basis. Decisions of such reviews are ratified by the entire IRB at the next full committee meeting.

4. Protocol Application

4.1 PROTOCOL SUBMISSION

All investigators must submit an Initial Query or a Full Application through the IRB Protocol Application System (PAS). An Initial Query is a shortened, partial application that may be used to determine if a research study is considered human subjects research or not, if it qualifies as exempt research, or if additional information is required. Investigators are encouraged to read pertinent background information available on the IRB website (irb.caltech.edu) and to contact the IRB Administrator with questions, prior to submitting a protocol application. Investigators must adhere to specific deadlines regarding receipt of materials by the IRB, in order for their protocol to be considered at an upcoming IRB meeting.

4.2 ELEMENTS OF THE PROTOCOL APPLICATION

The protocol application can be found online (access.caltech.edu – Research Services – IRB Protocol Application System). It is important that investigators provide a clearly written protocol that conveys sufficient information so that the IRB can evaluate the risks and benefits to the study participants. Pasting information from a grant application is generally insufficient. Investigators should focus on providing a clear, accessible description of what they will do, and ensure that they carefully identify and address the risks and benefits involved with the research. A protocol application includes the following components listed below. Failure to provide the components listed may delay review of a protocol.

1. The name and contact information for the Principal Investigator (PI) and personnel on the study.
    - All PIs and personnel are subject to the training requirements pursuant to section V(A)(2)(d).
    - The IRB may permit minors who are at least 16 years old to work, volunteer or intern in positions that involve the testing of human subjects when certain additional requirements are met. Follow IRB SOP: *Minors Working with the IRB*.
2. Description of participant involvement, including:
    - a description of participation in the research, including a description of how they are recruited (e.g., through advertisements), who participants are (e.g., college students), whether they include vulnerable populations, how many are anticipated (sample size), statistical rationale for sample size, and what the participants will experience during the study session. This needs to be in accessible, clear language, and it needs to provide sufficient information so that an IRB member who is not a scientist can understand the protocol (similar to what a participant would expect). Describe the types of stimuli that might be used, the tasks requested of the participants, and the types of

dependent measures collected. Any associated apparatus, device, or equipment for data collection must be described. The nature of the stimuli, tasks, and collected measures must be described in sufficient detail to allow the IRB to evaluate their possible risks, psychological and physical, in relation to the claimed scientific benefits of the study (see section iv below for additional information). Copies of questionnaires, surveys or other tools that will be used must be provided. Follow IRB SOP*: Recruitment Materials*.

- a description of the identifiability of the data. Provide details on the safety and security of identifiable data/specimens where the subject identity may readily be ascertained by the investigator or is associated with the biospecimen. Identifiability is described as follows:
    - Identifiable data: Information that identifies the participant are stored in the data set.
    - Coded data: Data are considered coded when they meet the following criteria:
        - Identifying information (such as a name or address/location) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and
        - A key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.
    - De-identified data: Data are considered de-identified when all direct or indirect identifiers or codes linking the data to the individual participant's identity are destroyed or broken, such that the investigator no longer has the ability to ascertain the identity of the participant.
    - Anonymized data: Data is anonymized when the data has been de-identified and the code no longer exists. Anonymization is intended to prevent participant re-identification.
    - Anonymous data: No identifying information was collected from the participants. Note that with small participant populations, such as those drawn from the Caltech community, a constellation of characteristics of a population may allow for individuals to be identified and the data may not be anonymous, even when no names or other personally identifying information are collected.

  Follow IRB SOP: *Anonymous, De-identified, & Coded Data*.

3. A full description of potential risks to the participants, as well as any benefits, together with a summary of why the investigator believes the benefits outweigh the risks (this includes potential psychological risks, such as emotional distress, physical risks, such as the potential for injury, social, economic, and

legal risks. Risks include potential harm, discomfort or inconvenience). The Investigator must explain how these risks compare to those commonly encountered in everyday life, how the risks will be minimized and how any residual risk is managed and outweighed by societal benefit.

- Minimal Risk means that 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.
- Greater Than Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are more than minimal risk.

4. When the research is a collaboration with another institution, descriptions of the research activities at each institution, a listing of the roles in the research for each personnel, and a statement as to which IRB(s) will review and approve the research. The application should include, as attachments, any relevant documentation, for example, the collaborator's IRB protocol, informed consent, and approval from the IRB of record or a statement that such approval is in process.
5. When appropriate, a statement that the PI has requested to work with the IRB Office to apply for a Certificate of Confidentiality (COC) in accordance with NIH provisions, or that a COC has been obtained from NIH.[5] COCs are automatically granted for all NIH-funded studies. Investigators should consider a COC if collecting sensitive information such as drug use, or information regarding civil and/or criminal proceedings, that could potentially be linked to the participants' identity.
6. Confirmation that all investigators involved in the conduct of human subjects research have completed the appropriate human subjects training (CITI or other training as required and approved by the IRB) within the last five years, or within the last three years for clinical trials or DOD-sponsored studies. Human subjects training is also required for research that is deemed exempt. The IRB may require investigators to complete new or additional human subjects training if there are changes in regulatory requirements or policy. CITI training modules are available at access.caltech.edu, under Research Services – Research Ethics Education (CITI).

[5] Generally, any justified IRB-approved research project may be eligible for a Certificate of Confidentiality from the National Institutes of Health. Federal funding is not a prerequisite for the NIH to issue a Certificate of Confidentiality, but the subject matter of the study must fall within a mission area of the NIH or the Department of Health and Human Services. Under federal law, a COC allows Caltech, the investigators, and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Projects that are NOT eligible for a Certificate are projects that are:

- not research,
- not collecting personally identifiable information,
- not reviewed and approved by the IRB as required by these guidelines, or
- collecting information that, if disclosed, would not significantly harm or damage the participant.

7. Identification of the funds used to support the study (funding source and Caltech PTA award number (if available).
8. A copy of the Informed Consent Form (ICF) and additional detail as outlined in IRB SOP: *Elements of the Informed Consent Form.*

The IRB Chair, IRB members, or the IRB Administrator acting on their behalf, may request additional materials as needed for review.

4.3 PROTOCOL AMENDMENTS

Protocol amendments must be submitted and approved by the IRB before any deviations from the protocol are made. Investigators are required to submit an amendment application in PAS setting forth a summary of the proposed modifications and indicate any change in the risks to participants associated with the modifications. Modifications involving changes to previously approved documents (e.g., ICF, recruitment materials) or the addition of new documents should be attached to the application. The modifications may be eligible for expedited or full committee review.

4.4 VULNERABLE POPULATIONS and SPECIAL CIRCUMSTANCES

Investigators must provide a rationale for the involvement of vulnerable populations in their research. When vulnerable populations are targeted for enrollment, the IRB assesses the additional safeguards proposed by the investigators to minimize the possible risk and the chance of harm to these populations. Research involving vulnerable[6], medically complex[7] populations, and other special circumstances may require additional human subjects training. The additional courses have been determined by the IRB and are available through CITI at access.caltech.edu.

MINORS (CHILDREN)

Research involving non-neonate participants, 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 a minor will be included in a human subjects study, the investigators who will be collecting data must meet requirements provided in Caltech’s Staff Personnel Memoranda on Minors (PM) and abide by Caltech’s Standards

[6] A vulnerable population is defined as including a recruitment pool of persons potentially subject to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

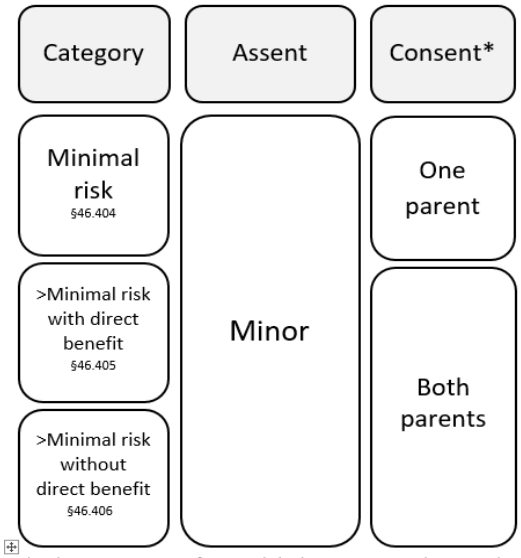
[7] Medically complex participants may include pregnant women, hemispherectomies, paraplegic people, and other conditions with complex care needs.

for Interacting with Minors (Standards). Meeting such requirements may include completion of online mandatory reporter training or submitting to a background check.

In addition to specialized informed consent requirements and human subjects protections for minors, there may be testing restrictions or requirements related to collecting data from minors imposed by the IRB based upon the Caltech PM or Standards, referenced above.

Research involving minor participants may be exempt from IRB review, as described in section 6.3 of this policy. As described in section 6.3, educational tests, surveys, interviews and observation of public behavior research with minors may be exempt ONLY when the research involves observations of the participants' public behavior AND the investigator is NOT participating in the activities being observed.

If the research on minors is not exempt from IRB review, the research will be reviewed by the IRB to ensure that all of the standard Caltech requirements for review and approval are met, as well as to ensure that (1) the consent process requires assent of the child, as well as the consent of at least one parent or guardian, and (2) the research does not involve greater than minimal risk unless the prospect of direct benefit to the participant justifies the risk or the research is likely to yield generalizable knowledge about the child's disorder or condition (see Figure).



When, in the judgment of the IRB, some or all of the minor participants are not capable of providing assent, the IRB may approve research where the assent of some or all of the participants is not required.

For research that involves only minimal risk, or a small increase over minimal risk where the prospect of direct benefit to the participant justifies the risk, consent of at least one parent is required. When the research involves a small increase over minimal risk and there is no prospect of direct benefit to individual participants to justify the risk, but where the research is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition, the consent of both parents is required 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. In

addition, 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. If the research meets these criteria, the IRB may elect to approve the research. If the research meets the criteria described in section 6.4, it may be approved in an expedited review.

PREGNANT WOMEN, HUMAN FETUSES, AND NEONATES

Research involving pregnant women, human fetuses, and neonates will be reviewed in a convened meeting of the IRB to ensure that all the standard Caltech requirements for review and approval are met as well as to ensure that the research is compliant with all federal regulations.

PLACENTA AND A NON-VIABLE FETUS, OR FETAL MATERIAL

Research involving placental material collected after delivery of the placenta, or a non-viable fetus or fetal material will be reviewed by the IRB to ensure compliance with applicable federal, state, and local laws and regulations for such activities. If the material is linked to individually identifiable information such that a living individual could be identified, directly or indirectly, through the identifiers, then the living individual will be considered a research subject and the protocol will be subject to review and approval pursuant to the standard Caltech IRB requirements.

PRISONERS

If a protocol involves an individual involuntarily confined or detained in a penal institution (prisoner), the IRB will invite the prisoner or a prisoner representative to participate in its review. Research involving prisoners will be reviewed at a convened IRB meeting to ensure that all the standard Caltech requirements for review and approval are met as well as to ensure that the research is compliant with all federal regulations.

STUDENTS AND LAB MEMBERS

Caltech students participating in Caltech courses taught or TA-ed by an investigator, or over whom the study investigator has significant authority (e.g. students living in housing where the investigator is a resident advisor) and lab members (including all students, postdocs, research and administrative staff, volunteers and visitors, as well as any Caltech personnel supervised by a Caltech investigator or over whom the study investigator has significant authority) as vulnerable populations. Even when investigators have no opinion about whether students and lab members participate, the students and lab members may nonetheless feel pressured or coerced

to do so. As such, investigators may not require a student or lab member to participate in research as a condition of a class or of employment, and students and lab members should not be selected solely on the basis of convenience. Follow IRB SOP: *Students and Lab Members as Study Participants*.

PHYSICAL CONTACT WITH PARTICIPANTS

Research may require the investigator to have physical contact with subjects. If physical contact is expected, the nature of the contact needs to be disclosed in the ICF. In general, for the safety and security of both the participants and the investigators, investigators should avoid one-on-one situations where physical contact is expected, be aware of situations which actions can be misconstrued by others, be professional and maintain high standards of personal behavior at all times, maintain appropriate physical boundaries at all times and touch subjects only when necessary and only in ways that are appropriate, public and non-sexual. When physical contact with a participant is expected, two attentive investigators must be in the room for all portions of the study where there is to be physical contact between an investigator and a participant. Exceptions to this policy will be reviewed on a case-by-case basis. Follow IRB SOP: *Physical Contact with Study Participants*.

RESEARCH INVOLVING THE USE OF INSTITUTIONAL DATA

Institutional Data include data generated by Caltech through the course of its business or teaching, including de-identified data. Institute policy, based upon a memo issued by Caltech leadership in 2020, requires that PIs wishing to use Institutional Data in their research obtain approval for the use of such data from Institutional Approvers.

To facilitate the approval process and to ensure the proper consideration of human subjects protection, PIs wishing to use Institutional Data must submit a query describing the data requested, indicating the campus population (student, staff, postdoc, faculty or a combination), explaining how the data will be obtained, stored, used in analysis and reported, and describing how the PI will employ best efforts to provide notice to or obtain consent from the participants whose data is being used, or a justification of why there will be no notice or consent. A subcommittee of the IRB will meet with the appropriate Institutional Approver and a decision will be made as to whether or not the Institutional Data may be used for this purpose. Follow IRB SOP: *Institutional Data*.

INCIDENTAL FINDINGS

Human subjects research may sometimes yield findings concerning individual research participants that have potential health importance but are beyond the aims of the study. Such findings are known as Incidental Findings

(IFs). Caltech policy requires investigators to identify in their protocol applications whether their studies are likely to yield IFs.

If a study is likely to yield IFs, the investigator will be asked in the protocol application to identify the categories of IFs the study is likely to yield (e.g., serious and actionable IFs; serious and non-actionable IFs; non-serious and actionable IFs; and non-serious and non-actionable IFs). The IRB requires that all serious and actionable IRFs be reported to research participants. Investigators may decide how all other IFs are handled, whether or not they are reported to participants or whether the investigator wants to give the participant the option to learn of the IF. Investigators whose studies are likely to yield IFs must also describe in their protocols how IFs will be handled. Finally, investigators who intend to report IFs to participants must include language in their ICFs informing participants of which categories of IFs will be reported and/or, if applicable, providing participants with the option to elect which categories of IFs, if any, to be informed of. Follow *SOP 8: Incidental Findings* .

4.5 FDA-REGULATED RESEARCH: RESEARCH ON DEVICES

All studies of investigational devices, unless not subject to or exempt from the regulation, must have an Abbreviated Investigational Device Exemption approved by the IRB for Non-Significant Risk (NSR) devices, or a Full Investigational Device Exemption approved by the IRB and FDA for Significant Risk (SR) devices before the study may begin.[8] An approved Investigational Device Exemption (IDE) allows for the discovery and development of useful devices intended for human use without FDA premarket approval for sale or meeting regulatory performance standards. A PI must submit an IDE application to the FDA to use a significant risk device in a study and may not begin the study until the IDE is approved (21 C.F.R. § 812.20).

PIs conducting research that involves the use of an investigational medical device must complete the applicable Devices section of the IRB protocol application. Investigators must provide sufficient information about the device, including the suggested risk level classification. The IRB will determine whether the study is subject to or exempt from IDE requirements.

The IRB can assist investigators in preparing the necessary documentation for an IDE application.

Whether studies on medical devices involving study participants may be conducted on campus or at JPL depends on the level of risk to the participants. All studies involving FDA-regulated research must be done in accordance

[8] Devices in this context are medical devices, including instruments, apparatuses, and implants that are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease (21 U.S.C. § 321(h)).

with all the applicable regulations, Caltech policies described in this document and IRB SOP: *Investigational Devices*.

RISK CLASSIFICATION FOR DEVICES

- Significant Risk Device: An investigational device that (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant; (2) is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a participant; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a participant; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant. SR devices must have a Full IDE, 510(k) premarket notification to the FDA, premarket approval (PMA), humanitarian device exemption (HDE), or similar approval from the FDA before a study may proceed.
- Non-Significant Risk Device: An investigational device that does not meet the definition of a SR device and does not pose a significant risk to participants. If the IRB determines that the device is NSR, there is no requirement for submission of an IDE application to the FDA and the study may be conducted in accordance with FDA Abbreviated IDE requirements [§812.2(b)(1)]. If the IRB determines that a device is SR, and the PI had proposed that the IRB consider the device NSR, the PI shall submit to FDA a report of the IRB's determination within 5 working days. The FDA considers an investigation of a NSR device to have an approved IDE when the IRB concurs with the NSR determination and approves the study. No work may be performed under the study until both FDA and Caltech approvals are in place.
- Exempt devices: These devices do not pose significant risk to participants and are exempt from the requirements of 21 C.F.R. § 812.2(b). Exempt devices fall into the following categories:
    - A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
    - A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that it is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E or part 807 in determining substantial equivalence.

- A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing (1) is noninvasive, (2) does not require an invasive sampling procedure that presents significant risk, (3) does not by design or intention introduce energy into a subject, and (4) is not used as a diagnostic product or procedure.
- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
- A device intended solely for veterinary use.
- A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).
- A custom device as defined 812.3(b) unless the device is being used to determine safety or effectiveness for commercial distribution.

DETERMINING THE RISK CLASSIFICATION

The Caltech IRB has the responsibility to determine the risk level of an investigational device. The IRB shall rely upon the FDA determination when available, as well as the information provided in the protocol, and any additional information provided by the PI.

If there has been a determination of SR by the FDA, the study will be treated as a SR study under these policies. If the PI considers the device to be a SR Device and has submitted an application for an IDE (or its equivalent) to the FDA, the IRB shall wait for the IDE approval from the FDA to review the protocol for approval.

STUDIES ON SIGNIFICANT RISK DEVICES

Similar to studies involving drugs and biologics, studies of SR devices developed at Caltech cannot be conducted on campus or at JPL. Such studies may only be conducted off site, pursuant to a written agreement with a collaborator at a medical institution with adequate facilities, significant clinical trial experience, and appropriate medical expertise or by contracting the services of a professional clinical research organization. Caltech must enter into a formal agreement with the IRB of the collaborating medical institution or clinical research organization to agree to either joint review or rely on the external institution or organization's IRB review of the protocol. The external IRB must be properly constituted according to all regulations and must include members with appropriate expertise for the study. Notice of the external IRB's determination will be provided to the Caltech IRB in accordance with the joint review or reliance agreement. The protocol must be approved by one or both IRBs (as appropriate) before the study may begin.

STUDIES ON NON-SIGNIFICANT RISK DEVICES

If the IRB makes the determination that the study involves a NSR device, the IRB may approve the study.

The IRB may review protocols for studies on NSR and exempt devices developed at Caltech to be conducted on campus and at JPL. However, the IRB may also opt for an external IRB review or may require that a collaborator at a medical institution or an external professional clinical research organization be involved in the study.

5. Informed Consent

5.1 ELEMENTS OF THE INFORMED CONSENT FORM

The Informed Consent Form (ICF) typically follows the template generated in the IRB PAS. Investigators are responsible for editing their ICF, and ensuring that all text is easily understandable, is generally well written, and provides a prospective participant with the key information that is most likely to assist them in understanding why one might or might not want to participate in the research. Generally, ICFs for adults should be written at an eighth-grade comprehension level, though the level may be higher or lower based on the participant population. Scientific or technical terms, if necessary, should be defined in lay language. It is essential that the ICF is clear, simple, and in grammatically flawless English. Follow IRB SOP: *Elements of the Informed Consent*.

1. Research Description
2. Reasonably Foreseeable Risks
3. Benefits
4. Alternative Procedures or Treatment
5. Confidentiality of Record
6. Compensation and Treatment for Injury
7. Contact Information
8. Voluntary Participation
9. Support
10. Conflicts of Interest
11. Date of Approval/Expiration Date
12. No Clinically Relevant Research Results
13. Number of Participants
14. Withdrawal Procedures for Studies Subject to the General Data Protection Regulation (GDPR) of the European Union (EU) or the European Economic Area (EEA) and the Personal Information Protection Law (PIPL). Follow IRB SOP: *GDPR / PIPL*.

Depending on the nature of the research, additional elements may be required in the ICF as well:

1. Unforeseeable Risks
2. Termination of Participation by the PI
3. Additional Costs
4. Consequences of Participant's Withdrawal

5. Significant New Findings
6. California Experimental Subject's Bill of Rights
7. Incidental Findings
8. HIPAA Authorization
9. Photographing and Recording
10. Physical Contact
11. Fasting
12. Future Contact to Continue Data Collection
13. Data Management and Sharing
14. Commercial Use
15. Biospecimens
16. Broad Consent

See section 4.4 for a discussion of additional informed consent requirements for research involving minors.

5.2 DOCUMENTING INFORMED CONSENT

Unless otherwise approved by the IRB, informed consent shall be documented using a written IRB approved ICF and signed (including in an electronic format) by the participant or the participant's legally authorized representative. The ICF should be provided in advance of obtaining the signature in order to provide the participant or the legally authorized representative adequate opportunity to review the document. After signing, a written copy shall be given to the person signing the ICF for their records.

In some instances, oral, rather than written informed consent is appropriate. If the IRB approves oral consent, the investigator must prepare a written summary of the procedures to review with the participant or their legal representative as well as a short-written form for the participant or their legal representative to sign. If consent is given orally, a witness must also be in attendance.

The IRB may approve a waiver of the requirement of the PI to obtain a signed informed consent for some or all the participants if it finds any of the following:

1. The only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each participant (or legally authorized representative) should be asked if the participant wants documentation linking the participant's research, and the participant's decision will govern; or

2. The research presents no more than minimal risk of harm to the participant and involves no procedures for which written consent is normally required outside of the research context; or
3. If the participant (or legal representative) is a member of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to the participant and provided that there is an appropriate alternative mechanism for documenting that informed consent was obtained.
4. If a protocol requires the participant to fast for any length of time prior to arriving for the study, prior to participating in the study and/or prior to providing formal informed consent, the researcher must receive general consent from the participant before the participant begins to fast. Follow IRB SOP: *Fasting in Human Subjects Research*.

   Under these circumstances, the following additional criteria must be met:

   - Any recruitment materials describing the study must disclose that the study requires fasting. Indicate if fasting is an element of the screening process or fasting will be part of the study tasks once enrolled. The recruitment materials must also provide the total length of time for the fast which includes the time from the start of the fast through the experimental procedure time during which food is withheld.
   - During recruitment, participants should consent to fasting and the consent should be documented. This general consent can be obtained over the phone (during a screening interview) or by email.

In cases in which the documentation requirement is waived the IRB may require the investigator to provide the participant with a written statement regarding the research.

5.3 APPLICATION FOR WAIVER OR ALTERATION OF AN ICF

Informed consent documents generally must meet the requirements provided above; however, there are conditions under which the IRB may approve a consent procedure that alters the informed consent or waives the consent procedure, altogether.

WAIVER

The IRB may waive the requirement to obtain informed consent for research provided that the IRB satisfies either (1) or (2), under section Alteration, below.

ALTERATION

The IRB may not omit or alter the general requirements for informed consent, which include prospectively seeking consent from the participant (or the legally authorized representative), in language understandable to the participant, providing the participant with key information to help the participant consider whether or not they will participate, and minimizing the opportunity for coercion, and excluding exculpatory language. The IRB may not omit or alter the general requirements for broad consent, including consent for the storage maintenance or secondary research use for the identifiable private information or identifiable biospecimens, as described above. However, the IRB may approve a consent procedure that omits some or alters some or all of the other elements of informed consent provided that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (1) public benefit or service programs; (2) procedures for obtaining benefits or services under those programs; (3) possible changes in or alternatives to those programs or procedures; or (4) possible changes in methods or levels of payment for benefits or services under those programs; and (5) the research could not practicably be carried out without the waiver or alteration; or
2. The research involves no more than minimal risk to the participants; the research could not practicably be carried out without the waiver or alteration[9], the waiver or alteration will not adversely affect the rights and welfare of the participants, and whenever appropriate, the participants will be provided with additional pertinent information after participation.

In cases where the IRB approves a protocol with a waiver or alteration of informed consent, it may require the investigators to provide participants with a written statement regarding the research, sponsorship, and any conflicts of interest when applicable. Common examples where informed consent may be waived include the collection of questionnaire-based data over the internet or in classrooms.

[9] If the research involves using identifiable private information or identifiable biospecimens, a waiver or alteration can only occur if the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

6. Protocol Review

6.1 PROTOCOL CLASSIFICATION BY THE IRB

All Caltech human subjects research must be prospectively reviewed by the IRB. No previously approved human subjects research may be continued beyond the expiration date without prospective approval.

The IRB retains ultimate authority to determine whether a study meets the definition of human subjects research. The IRB Chair, sometimes in consultation with other IRB members, will determine whether the research described in the protocol qualifies as exempt from, for expedited, or for full committee review. The IRB Chair, sometimes in consultation with the IO or members of the IRB, will determine if the protocol describes FDA-regulated research, and if so, it will be reviewed accordingly. The IRB Chair, in consultation with the IO, will also determine whether a protocol can be approved on the basis of review by another Institution's IRB (Reliance).

6.2 PROTOCOL REVIEW BY THE IRB

Appropriate review of the application and informed consent process requires that the IRB:

1. determine whether the risk to human subjects is minimized;
2. determine whether the risk to the subjects is reasonable in relation to anticipated benefits, if any, and the importance of the knowledge potentially gained from the research;
3. determine whether selection of the participants is equitable and justified for the particular study being conducted;
4. determine whether the ICF itself meets the criteria specified in this Policy;
5. determine whether the procedure seeking informed consent from each subject is appropriate, and when applicable, whether a waiver of informed consent or an abbreviated informed consent can be granted;
6. determine whether the investigators have a method for appropriately documenting the informed consent;
7. determine whether there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data;
8. determine whether the protocol has adequate provisions for monitoring data collected to ensure the safety of participants;
9. determine whether some or all of the participants are likely to be vulnerable to coercion or undue influence. Should participants be vulnerable, the IRB shall determine whether additional safeguards have been included in the study to protect the rights and welfare of these participants; and

10. for FDA-regulated research, determine if any of the research involving human subjects may be conducted on campus or at JPL, or if it must be conducted at another institution or organization with appropriate facilities and expertise.

6.3 EXEMPT RESEARCH

In accordance with federal regulations, certain research involving human subjects is exempt from most of the requirements of the Federal Policy for the Protection of Human Subjects, but is still considered research requiring IRB review for an exemption determination. If a PI believes their research qualifies for exemption, they should submit an Initial Query through the IRB PAS, describing the project and identifying the likely basis for the exemption.

Certain categories of participants do not qualify for these exemptions. Research with prisoners, under Subpart C of 45 C.F.R. 46 does not qualify as exempt, except for research aimed at involving a broader participant population that only incidentally includes prisoners. Exemption 3 does not apply to research with children, under Subpart D of 45 C.F.R. 46. Exemption 2 (i) and (ii) only apply to research involving educational tests or the observation of public behavior when the investigators are not participating in the activities being observed.

An exemption from IRB review may be available for the following categories of research:

- Exemption 1: Research conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction is exempt. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. (45 C.F.R. § 46.104(d)(1)).
- Exemption 2: Research that only includes interactions involving educational tests (e.g., cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (not including visual or auditory recording) is exempt if at least one of the following criteria are met:
    i. The information obtained is recorded in such a manner that the identity of the participants cannot be readily ascertained, directly or through identifiers linked to the subject (45 C.F.R. § 46.104(d)(2)(i));

ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation (45 C.F.R. § 46.104(d)(2)(ii)); or

iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review[10] to ensure that, when appropriate, adequate provisions to protect the privacy of subjects and maintain the confidentiality of data are in place. (45 C.F.R. § 46.104(d)(2)(iii))

- Exemption 3:

i. Research involving benign behavioral interventions[11] in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording is exempt if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

A. The information obtained is recorded in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subject (45 C.F.R. § 46.104(d)(3)(i)(A));

B. The disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement or reputation (45 C.F.R. § 46.104(d)(3)(i)(B)); or

C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects and the IRB conducts a limited IRB review to ensure that, when appropriate, adequate provisions to protect the privacy of subjects and maintain the confidentiality of data are in place (45 C.F.R. § 46.104(d)(3)(i)(C))

[10] Limited IRB review is a process that is required only for certain exemptions and does not require an IRB to consider all the IRB approval criteria in §46.111. In limited IRB review, the IRB must determine that certain conditions, which are specified in the regulations, are met. Limited IRB review may be done via the expedited review mechanism, that is, by the Chair or an experienced IRB member designated by the Chair (although it can also be conducted by the full IRB). Continuing review is not required. [Refer to sections 45 CFR 46.109(a) and 46.109(f)(1)(ii) of the revised Common Rule.]

[11] Benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subject and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Benign behavioral interventions may include having subjects play online games, solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of receive cash between themselves and someone else.

ii. If the research involves deceiving the subjects regarding the nature or purpose of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that they will be aware of or misled regarding the nature or purposes of the research.

- Exemption 4: Secondary Research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens is exempt if at least one of the following criteria is met:
  i. The identifiable private information or identifiable biospecimens are publicly available (45 C.F.R. § 46.104(d)(4)(i)); or
  ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify the subjects (45 C.F.R. § 46.104(d)(4)(ii)); or
  iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 C.F.R. parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 C.F.R. §164.501 or for "public health activities and purposes" as described under 45 C.F.R. § 164.512(b); or
  iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the Paperwork Reduction Act of 1995, 44 USC 3501 et seq.
- Exemption 5: Research or demonstration projects conducted or supported by a Federal department or agency, or otherwise subject to the approval of a US department or agency head designed to study, evaluate, improve, or otherwise examine (1) public benefit or services programs, (2) procedures for obtaining benefits under these programs, (3) possible changes or alternatives to those programs or procedures, or (4) possible changes in methods or levels of payment for benefits or services under those programs. (45 C.F.R. § 46.104(d)(5))

- Exemption 6: Taste and quality food evaluation and consumer acceptance studies are exempt (1) if wholesome foods without additives are consumed, or (2) if a food consumed that contains a food ingredient at or below the level and for a use found to be safe, agricultural chemical or environmental containment at or below the level found to be safe, by the FDA or approved by the EPA or the Food Safety and Inspection Service of the U.S. Department of Agriculture. (45 C.F.R. § 46.104(d)(6))
- Exemption 7: Storage or maintenance for secondary research for which Broad Consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use is exempt, provided that the IRB conducts a limited IRB review and makes the determination that Broad Consent is in accordance with the requirements for Broad Consent in this policy and that it is appropriately documented (or waiver of documentation is appropriate) and if there is a change made, for research purposes, in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of the subjects and to maintain the confidentiality of the data. (45 C.F.R. § 46.104(d)(7))
- Exemption 8: Secondary research for which Broad Consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research is exempt if (1) Broad Consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with this policy, (2) the Broad Consent is documented or waiver of documentation was obtained and (3) the IRB conducts a limited review and makes the determination that the research to be conducted is within the scope of the Broad Consent referenced in this policy, and (4) the investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results. (45 C.F.R. § 46.104(d)(8))

DETERMINATIONS

If research qualifies as exempt, it will be reviewed by the IRB Chair in consultation with other members of the IRB, as needed. Exempt protocols may require an appropriate notice and/or ICF may still be required by Caltech to fulfill obligations outside of the purview of the IRB. Investigators are obligated to inform the IRB if their exempt protocol changes that might impact the IRB exemption determination.

6.4 EXPEDITED REVIEW

Expedited review typically applies to protocols that involve no more than minimal risk, and to protocols that involve well established and approved procedures (http://www.hhs.gov/ohrp/policy/expedited98.html). Expedited review cannot be used if the identification of the study participants would reasonably place them at

risk of liability or be damaging to the participants in any way; or the research is classified. The following may qualify for expedited review:

- Category 1: Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- Category 2: Collection of blood by finger, heel, ear or superficial or peripheral venipuncture, subject to height and weight requirements, provided an appropriate written contract is in place with a licensed, insured medical professional who will collect the blood[12].
- Category 3: Prospective collection of biological specimens by non-invasive means.
- Category 4: Collection of data through non-invasive procedures routinely employed in clinical practice, except for X-rays, microwaves or MRI.
- Category 5: Collection of materials that have been already previously produced for non-research purposes, such as materials used for medical treatment or diagnosis.
- Category 6: Data from voice, digital, or image recordings made for research purposes, provided that the participants are not identifiable.
- Category 7: Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs, or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies (which may qualify as Exempt Research as well).
- Category 8: Continuing review of research previously approved by the convened IRB as follows:
    a. Where (i) the research is permanently closed to the enrollment of new participants (ii) all participants have completed all research-related interventions, and (iii) the research remains active only for long-term follow-up of participants; or
    b. Where no participants have been enrolled and no additional risks have been identified; or
    c. Where the remaining research activities are limited to data analysis.
- Category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two through eight do not apply, but the IRB has

[12] Research eligible for expedited review are listed in Categories in the Federal Register, November 9, 1998 (Vol. 63, No. 216, pp. 60364-67). The Caltech IRB has opted not to exempt Category 1, which is for research on drugs and medical devices meeting certain criteria.

determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

- Amendments: Amendments to previously approved protocols that involve minor changes that introduce no additional risk in previously approved research for no longer than the protocol's previously approved time period.

DETERMINATIONS

If research qualifies for expedited review, it will be reviewed by the IRB Chair, by an IRB member designated by the Chair, or by a subcommittee designated by the IRB Chair, in consultation with other members of the IRB as needed. Expedited review considers the protocol application using the same criteria as would be used by the full IRB and may either approve, require modification to, or refer the research to the full convened IRB for review.

6.5 FULL COMMITTEE REVIEW

Studies that involve greater than minimal risk to participants and studies that do not meet the criteria for expedited review require review at a convened board meeting, also referred to as full committee review. Regardless of risk level, the IRB may require full committee review when the research involves vulnerable populations (particularly prisoners), sensitive topics that may require additional protections, or a complex research design requiring the expertise of multiple IRB members to evaluate. At any time during the review process, any IRB member can request that a protocol undergo full committee review.

DETERMINATIONS

After review, the IRB will vote to approve, disapprove, require modifications for approval of the protocol, or defer the protocol. The IRB may also formally approve protocols but require further approvals for the research to begin. In order for research to be approved, it must receive the approval of a majority of the members present at the meeting.

Research covered by this Policy that has been approved by the IRB may be subject to further review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by the IRB.

RATIFICATIONS

The IRB will ratify exempt protocols and protocols reviewed via expedited review at the next IRB meeting or subject the protocols to further review. Any member at the full committee meeting may request a detailed explanation of an exempt or expedited protocol approval to clarify any questions related to that approval.

6.6 CONTINUING REVIEW

All non-exempt protocols are reviewed at least annually after initial approval and may be renewed four times (for a total of five years). In instances where the IRB determines that there may be additional risk to participants or that participants may be vulnerable, the IRB may require review twice a year or at a frequency appropriate to the degree of risk. Continuing review may be expedited. In cases where a protocol was reviewed and approved by an external IRB, annual review from that external IRB is required and documentation should be attached to the protocol renewal application in PAS prior to work continuing at Caltech.

The IRB may choose to review studies that were previously reviewed and approved by the IRB as expedited in its continuing review. Studies that meet the following criteria may qualify for expedited continuing review:

1. there have been no or minor changes in a protocol that was previously approved under expedited review during the period for which the approval is authorized,
2. there have been no or minor changes in a previously approved protocol, and no relevant new information concerning that protocol (such as any reported adverse events or any other information suggesting changes in risk),
3. the research is permanently closed to enrollment of new subjects, all subjects have completed all research-related interventions and the research remains active only for long-term follow-up of subjects,
4. no subjects have been enrolled and no additional risks have been identified, or
5. the remaining research activities are limited to data analysis.

PIs will be notified at least 30 days before the expiration of a protocol requiring annual renewal, or de novo application. An annual renewal or de novo application must be reviewed and approved before the expiration date of the protocol (one year minus 1 day after the previous approval). If an IRB approval expires, all procedures related to the protocol must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of identifiable private information. If a renewal or de novo application is pending or in review, the activity involving study participants under the protocol may not resume until the IRB has reviewed and approved the protocol.

6.7 NOTICE

After the IRB has reviewed the protocol application and made a final determination, it will notify the PI and the IO in writing of its decision. The IRB will also notify the investigators as to whether subsequent protocol review will be annual on approved protocols, or more frequently, pursuant to Continuing Review. If the IRB decides to

disapprove a protocol application, the IRB will provide the investigator with a statement of the reasons for its decision and an opportunity to respond.

6.8 REVIEW OF STUDIES CONDUCTED BY UNDERGRADUATE OR GRADUATE STUDENTS FOR COURSE CREDIT

Although studies involving study participants in undergraduate and graduate courses typically do not meet the regulatory definition of research, Caltech's IRB should review the study before it is conducted. Protocol review of classroom studies may be considered by the IRB as exempt research. All classroom projects involved surveys or procedures involving study participants should submit a query through the IRB PAS.

6.9 PILOT STUDIES

A pilot study is an initial investigation into the viability of a research project or the refinement of a research project, conducted on a limited scale, typically involving 10 or fewer participants, and characterized by its exploratory nature. Its primary purpose is to assist the investigator in fine-tuning data collection procedures and instruments, or in developing a more refined and precise research design. Compensation is not required for participants of pilot studies. Data from or about participants in a pilot study may not be published and, as such, a pilot study does not contribute to generalizable knowledge, and is therefore not classified as human subjects research. It is important to note that data regarding the design of the research project or instruments, devices or other equipment used in the research, or conclusions obtained from the pilot study (for instance, the stimuli that were chosen for the actual research study), devoid of participant data, is publishable.

There are certain circumstances where pilot studies require the submission of an IRB Initial Query in the IRB Protocol Application System (PAS). Those circumstances are as follows:

1. Invasive procedures or testing of devices,
2. Physical or psychological distress,
3. Vulnerable populations, or
4. Sensitive information collected from the Caltech community

Follow IRB SOP: *Pilot Studies*

6.10 COOPERATIVE RESEARCH, RELIANCE ON ANOTHER IRB, AND SINGLE IRB REVIEW

Cooperative research projects are non-exempt research projects that involve more than one institution. In the conduct of cooperative research, each institution is responsible for safeguarding the rights and welfare of study participants and for complying with federal regulations.

The Caltech IRB may rely on an IRB at another institution by entering into a formal reliance agreement. Similarly, the Caltech IRB may allow another institution to rely on it for protocol review through a formal reliance agreement. The formal reliance agreement should be executed through SMART IRB for institutions that participate in SMART IRB, or by a written agreement documenting (1) the relying institution's reliance on the other IRB for oversight of the research, and (2) the responsibilities that each institution will undertake to ensure compliance with applicable federal, state and local regulations as well as this policy. The reliance agreement may take the form of an IRB Authorization Agreement, participation in a consortium, or use of a commercial IRB.

For cooperative research not funded by a federal agency, reliance may be practical when the study is done with a collaborator at another institution or the interaction with the study participants is conducted at another institution. For such cooperative research carried out at multiple institutions, it may be most efficient for a single IRB to do all the review. The documentation requirements for such reliance agreements are the same as for federally funded research.

For cooperative research not funded by a federal agency, the Caltech IRB may elect to jointly review an IRB protocol with an IRB from another institution when duplication of effort is warranted. Joint IRB review may be practical when both IRBs have particular expertise that is required to review a particular protocol, and when required by the funding agency. However, it is expected that in general it will be preferable to have a single IRB of record.

The decision to enter into reliance with another IRB or to implement joint IRB review may be made by the Chair, in consultation with the IO, or can be delegated to a subcommittee.

Reliance and cooperative research agreements when Caltech is relying on another institution's IRB may require the Caltech PI to submit a Caltech IRB application as a query or a full application with all the supporting documentation attached to the Caltech application (including but not limited to other institute IRB approval/ICF/application, reliance agreement, grants or other contracts, recruitment materials, etc.). With these types of cooperative research/reliance protocols, the Caltech IRB will have an informational review and discussion of the application and provide feedback to the PI. The Caltech IRB will agree not to approve or disapprove a protocol when relying on another institution's IRB. If another institution wishes to rely upon the Caltech IRB, the protocol will be reviewed in accordance with full committee review requirements.

Since Caltech does not have research medical or hospital facilities, in vivo human testing of new drugs and biologics developed at Caltech cannot be conducted on campus or at JPL.[13] Such studies may only be conducted off site, either pursuant to a written agreement with a collaborator at a medical institution with adequate facilities, significant clinical trial experience and appropriate medical expertise, or by contracting the services of a professional clinical research organization. Caltech must enter into a formal agreement with the IRB of the collaborating medical institution or clinical research organization agreeing to either jointly review or rely on the external institution or organization's IRB review of the protocol.

6.11 DELAYED ONSET OF RESEARCH OR 118 DETERMINATION MEMO

Section 45 CFR § 690.118 of the Federal Policy for the Protection of Human Subjects and 45 CFR 46.118 of the Common Rule state that certain types of applications for grants, cooperative agreements, or contracts are submitted to Federal departments or agencies with the knowledge that participants may be involved within the period of support, but where definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving participants remain to be selected; and projects in which participant involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. Except for research waived under §46.101(i) or exempted under §46.104, no participants may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Federal department or agency component supporting the research.

A funding agency may request that the PI provide a memo or notification of the "Delayed Onset of Research" or a "118 Determination Memo". The decision to grant a "118 Determination" can be made by the Chair, the IO, or the IRB Administrator in consultation with the IO. The initial application for a "118 Determination" will require the Caltech PI to submit an Initial Query with all the supporting documentation attached to the Caltech application (including but not limited to the proposal, and the specific request from the federal granting agency for a "118 Determination" memo, if applicable). It is recommended that investigators consult with the IRB when drafting a proposal to verify that a "118 Determination" is appropriate for the study. Follow IRB SOP: *118 Determination Memo*

[13] Drugs include articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and articles (other than food) intended to affect the structure or any function of the body (21 U.S.C. § 321(g)(1)).
Biological products include viruses, therapeutic serums, toxins, antitoxins, vaccines, blood, blood components and derivatives, allergenic products, proteins (except chemically synthesized polypeptides) applicable to the prevention, treatment, or cure of a disease or condition (42 U.S.C. § 262(i)). Some biological products, commonly referred to as biologics, also meet the regulatory definition of drug.

7. Responsibilities, Noncompliance, Protocol Deviations & Violations

7.1 RESPONSIBILITIES

The responsibility for compliance with the policies of the IRB rests, first and foremost, with the PI. Each PI must be educated regarding basic knowledge of ethical research with study participants, adhere to the timely submission of required documents to the IRB, and ensure compliance with rules and regulations among the research team.

The PI is responsible for ensuring that all investigators and personnel who interact with study participants in the context of research complete the online CITI human subjects training before beginning research and renew this training every five (5) years thereafter, or every three (3) years thereafter for clinical trials or DoD-funded studies. Such training provides a basic background in ethical research practices. The Caltech IRB provides additional educational materials on its website that all investigators are encouraged to review.

The Caltech PI is responsible for submissions of protocols and responding to IRB requests. Failure to submit protocols in a timely manner or respond to IRB requests may result in delays in research or withholding of research funds. Failure to respond to an IRB memorandum requiring response within 30 days may result in closure of a pending or active protocol.

Finally, the Caltech PI is responsible for ensuring that the entire research project and all personnel associated with it comply with this policy and all applicable rules and regulations.

The IRB has authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements (non-compliances, protocol deviations and violations) or that has been associated with unexpected serious harm to participants (resulting from unanticipated problems and other events).

7.2 NONCOMPLIANCE

Should a PI or investigator be non-compliant with these policies or an approved IRB protocol, the IRB Chair shall issue an immediate notice for correction and determine whether the noncompliance is serious. Examples of noncompliance which rise to the level of serious include, but are not limited to, failure to obtain informed consent, and substantive modification of protocols or informed consent documents without IRB approval. The Chair will report the noncompliance and any subsequent action to the Institutional Official as soon as possible, and to the entire IRB at the next convened meeting.

Should a PI fail to comply with this IRB Policy, fail to obtain appropriate IRB approval, or if there are recurring problems with one or more of a PI's protocols, the IRB Chair may call a meeting of the IRB or convene a subcommittee to review the violation or problem and determine whether it is appropriate to suspend or terminate the research.

OHRP may perform compliance oversight evaluations of Caltech's human subjects research and restrict or attach conditions to the FWA. Similarly, the FDA Commissioner may take administrative action, including disqualifying Caltech and/or the Caltech IRB if a determination is made that the IRB has refused or repeatedly failed to comply with applicable government regulations or if a noncompliance adversely affects the rights or welfare of the study participants in an investigation.

7.3 PROTOCOL DEVIATIONS

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of an approved study that is not consistent with the research protocol or consent document.

The following deviations are considered "serious deviations" and must be reported to the IRB Chair immediately:

- deviations that may affect the risk/benefit analysis of a study,
- deviations that may affect the rights, health, and/or welfare of a participant,
- deviations that may affect the safety and/or privacy of a participant,
- deviations that may affect a participant's willingness to participate.

The IRB Chair shall issue an immediate notice for correction and determine whether the deviation is serious. All protocol deviations must be reported by the PI to the IRB as soon as possible and as part of the continuing review. The Chair will report the resolution of the deviation to the Institutional Official as soon as possible and to the IRB at the next convened meeting.

7.4 PROTOCOL VIOLATIONS

A protocol violation is an intentional act in which the protocol is not followed. The IRB Chair shall issue an immediate notice for correction and determine whether the violation is serious. If the violation is determined to be serious, it shall be treated accordingly pursuant to the Caltech Policy. In any event, the PI will be expected to correct the violation immediately and will be required to disclose the violation in the continuing review. An intentional violation shall require the IRB Chair to immediately notify the Institutional Official and the IRB, to review the violation(s), and to derive an appropriate corrective action or to suspend or terminate the research.

In the case of a suspected or reported violation, all research connected with that violation must be suspended immediately until further notice from the IRB.

7.5 REPORTING

Protocol suspensions or terminations due to serious or continuing noncompliance, protocol deviations, or protocol violations will be reported by the IRB Chair to the PI, the IRB, and the Institutional Official, and must include a statement of reasons for the IRB's action. Caltech shall also promptly report the following to the research sponsor (e.g., funding agency), OHRP, and FDA (as required):

- instances resulting in risk to the participant,
- substantial compromise of the informed consent process,
- serious or continuing noncompliance regarding administrative matters such as the federal regulations,
- serious or continuing non-compliance with the requirements or determinations of the IRB, and
- protocol deviations or violations resulting in suspension or termination.

8. Unanticipated Problems and Other Events

8.1 DEFINITIONS

An Unanticipated Problem is an event that is unexpected considering the research procedures and the subject population under study and a problem that places subjects or others at a greater risk of harm or discomfort than was previously anticipated. An event may also be unanticipated if it is also serious and unexpected in either the nature of the event or the frequency or severity of the event.

An Adverse Event is an undesirable event experienced by a human research subject, irrespective of whether the event is anticipated.

An Unanticipated Adverse Device Effect means any Adverse Event caused by, or associated with, a device, including any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An Adverse Reaction means any Adverse Event caused by, or associated with, a drug or biologic.

The term "event" is used in this section to refer to adverse events, unanticipated adverse device effects, adverse reactions, unanticipated problems, as well as other incidents, experiences or outcomes that may be related to an unanticipated problem.

8.2 IRB EVALUATION AND REPORTING OF EVENTS

All suspected events must be immediately reported to the IRB Chair by the PI, and the IRB Chair will make a determination regarding the nature and classification of the event. The initial report shall include (1) the name of the PI, (2) the name of the research project, (3) the grant title and number (4) the IRB protocol number, (5) the nature of the event, and (6) any proposed corrective actions. Everyone, including co-Investigators, members of the Caltech community, human subjects, etc., are encouraged to report events to the IRB Chair or Caltech Hotline. The IRB Chair will notify the IO and keep the IO apprised of any developments.

INITIAL DETERMINATION

The IRB Chair will make an initial determination as to whether the event is serious and may ask the investigator to place the research on hold until a subcommittee of the IRB can be formed and meet to discuss the event. If the IRB Chair determines that the event is not serious, the IRB Chair will notify the PI that the research may

continue. If the event is serious, a subcommittee shall be formed to meet as soon as feasible, within 48 hours of receiving the initial report. The IO shall be notified of both serious and non-serious events as soon as possible.

SUBCOMMITTEE EVALUATION

The subcommittee shall meet to determine whether the event is related or possibly related to the research, whether it requires reporting to the OHRP or FDA, and whether the problem warrants suspension or termination of approval.

In considering whether an event is related to the research, the subcommittee shall consider (1) whether the event was solely related to either the underlying condition or disease under study (unrelated to research), or (2) whether there were other unrelated circumstances that caused the event (e.g., a car accident resulting in death would be unrelated). The subcommittee may request that the PI provide additional or more detailed information to assist with the evaluation.

Should the subcommittee determine that an event is not related to the research, the research will be reinstated and the event, if reportable, will be reported to the OHRP or FDA within 30 days of the research being reinstated.

Should the subcommittee determine that an event is related to the research, the event will be reported to the IO, the PI, and OHRP, FDA, and the sponsor (as applicable) when the following apply:

- the event is a reportable event under the OHRP or FDA regulations,
- the event is serious and unanticipated,
- the event is not serious and anticipated, but the event is occurring at a frequency or with greater severity than expected,
- the event involves risk to the subjects or others,
- the event has resulted in suspension or termination of IRB approval, or
- the event (whether serious or not) is going to lead to a change in the IRB's assessment of the risk/benefit balance and/or lead to substantive modifications of the informed consent document or research protocol.

Any suspension or termination of the IRB approval must include a statement of the reasons for the IRB's action.

The subcommittee will report the event and any subsequent action at the next convened IRB meeting for ratification. Any proposed changes to a research study in response to an event must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazards to subjects. If the changes are more than minor, a protocol amendment must be approved.

9. Reporting to OHRP and FDA

9.1 IRB MEMBERSHIP

A current list of IRB members must be submitted to the Office of Human Research Protections (OHRP) whenever there is a change in IRB membership, at the time of renewal of the FWA, and when any changes to the list requires an update to OHRP.

9.2 NONCOMPLIANCE, PROTOCOL DEVIATIONS, AND VIOLATIONS

All noncompliance, protocol deviations, and protocol violations shall be promptly reported by the IO as described above in Section VI(E).

9.3 SUSPENSIONS OR TERMINATIONS OF IRB APPROVAL

All suspensions or terminations of IRB approval shall be promptly reported by the IO as described in section 8.2.

10. IRB Recordkeeping

10.1 IRB MEMBERSHIP

A list of current IRB members must be retained in the IRB records. The list must identify members by name, earned degrees, representative capacity, indications of experience (professional licenses, etc.), any employment or other relationship between the member and Caltech.

10.2 IRB POLICY

The IRB will post this policy document on its website. All Investigators are encouraged to read this IRB Policy.

10.3 DOCUMENTATION OF IRB ACTIVITIES

The IRB will prepare and maintain adequate documentation of IRB activities, including:

- records of all IRB protocol applications, including research proposals reviewed, scientific evaluations (if any), approved informed consent documents that have been reviewed by the IRB,
- records of all continuing review summaries and other progress report documentation submitted by investigators,
- reports of any injuries to subjects, adverse or other events,
- statements of significant new findings developed during the course of the research which may relate to a subject's willingness to continue participation which were provided to the subject as described in the requirements for informed consent.
- minutes of IRB meetings, sufficient in detail to show attendance, actions taken by the IRB, voting on actions (including the number of members voting for, against, and abstaining), the bases for requiring changes in or disapproval of research, and a written summary of the discussion of controverted issues and their resolution,
- documentation of risk assessment of any study devices, noting its decision of significant risk, non---significant risk, or exempt in the meeting minutes,
- records of all correspondence between the IRB and the investigators,
- a list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution, and
- the written policy, procedures, and guidelines for the IRB.

Records shall be retained for at least three years after completion of the research, and according to the Caltech Records Retention Schedule. All records will be accessible for inspection and copying by authorized representatives of appropriate departments or agencies (e.g., OHRP, FDA).