Caltech

POLICY OF THE

CALTECH ADMINISTRATIVE COMMITTEE FOR THE PROTECTION OF HUMAN SUBJECTS

(INSTITUTIONAL REVIEW BOARD: IRB)

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Contents

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I. 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 researchers 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

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

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:

a. Respect for Persons: recognizing the personal dignity and autonomy of subjects, and providing special protection of those subjects with diminished autonomy. This is achieved through true free and informed consent. The Caltech IRB recognizes the need to explain a research study to prospective participants in language they can understand.

b. Beneficence: protecting subjects 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.

c. 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 subject sampling and generalizability are important aspects of research.

II. APPLICABILITY AND AUTHORITY

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

"Research" is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge[2]. "Human subject" is defined as 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].

"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.

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

Studies involving human subjects that have been approved by the IRB may be subject to further review by the Institute. The Institutional Official (Chief Research Policy Officer) 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

[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 subject 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 subject is or may readily be ascertained by the investigator or associated with the biospecimen.

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 Institutional Official, the individual who is legally authorized to act for Caltech and obligates Caltech to the terms of the FWA. 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 occasionally amended with changes in federal regulations. The IRB Chair may make revisions to the IRB Policy in consultation with the Institutional Official 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 explicit objections, the proposed change will be considered accepted, and this will be ratified at the next meeting.

III. IRB MEMBERSHIP

A. IN GENERAL

The members of the IRB are appointed by the Caltech President. The IRB must consist of at least five voting members. The members should have varying backgrounds in order to promote complete and adequate review of research activities commonly conducted by Caltech. The IRB members shall possess the professional competence necessary to review specific research activities and to ascertain the acceptability of proposed research in terms of Institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB should also be diverse, taking into consideration a balance of race, gender, cultural background, and sensitivity to issues such as community attitudes, and professional expertise. The IRB shall have at least one member who is not affiliated with Caltech, or part of the immediate family of a person affiliated with Caltech. The IRB shall include at least one member whose primary concerns are in non-scientific areas. Should the IRB regularly review research involving a vulnerable category of subjects, consideration shall be given to including a member who is knowledgeable about and experienced in working with these subjects. An IRB member may always request or suggest that an expert be included in protocol review.

To protect the privacy of research subjects, 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 human subjects, 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 (5) 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 human subjects.

B. SPECIFICALLY

1. VOTING MEMBERS

The Chair and Vice-Chair will be selected and appointed by the Caltech President. 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 of 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

2. EX OFFICIO MEMBERS

The Director of the Environment, 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 on matters the Committee has under consideration. The Legal Advisor participates in the Committee's deliberations, as appropriate, but shall not be a member of the Committee.

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

3. 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 at any time during a meeting. 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.

4. AD HOC OR 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 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, with the understanding that confidentiality applies.

5. TERM

IRB members shall be appointed for three-year terms and shall typically serve no more than two consecutive terms. However, the President may appoint an individual to additional terms, if such action be judged necessary for the Institute.

IV. MEETINGS

A. 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 including 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.

B. 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 room 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.

C. 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.

V. REVIEW AND APPROVAL OF RESEARCH

A. INITIAL REVIEW AND APPROVAL

1. PROTOCOL SUBMISSION

All investigators must submit an online Initial Query (a shortened, partial application that may be used to determine if a research study qualifies as exempt research or if additional information is required) or a Full Application including a sample Informed Consent Form (ICF), or a justification for alteration or waiver of ICF. An ICF may be required for research that qualifies as exempt. See Section V (B) for a description of research that may qualify as exempt. 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.

2. ELEMENTS OF THE PROTOCOL APPLICATION

The protocol application can be found online (access.caltech.edu - IRB Submission and Review module). 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 human subject.

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.

a. the name and contact information for the Principal Investigator (PI) and personnel on the study,

   i. A PI may be: a tenured or tenure-track professorial faculty; a research professor; a JPL investigator; or a Caltech Associate Director (or above).

   ii. All PIs and personnel are subject to the training requirements pursuant to section V(A)(2)(d).

   iii. The IRB permits 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.

      (i) A minor is any person under the age of 18 years. Under the provisions of state and federal law, as well as Caltech's Minors Personnel Memorandum ("Minors PM") and Caltech's Standards for Working with Minors (Standards), minors may not be employed, intern or volunteer in any hazardous occupations.

      In addition, pursuant to the Minors PM, minors working, interning or volunteering in laboratories must be approved by the Division Chair, or designee, in consultation with the supervising PI. Minors working in areas with restricted access must also be approved by the supervising Director. Minors working with regulated subjects or materials must obtain the permission of the appropriate Caltech administrative committee.

      Minors are allowed only to help administer research protocols that do not require special licenses or skills (e.g., they cannot drive a car, and no one under 21 can serve alcohol), they may administer only protocols that are exempt or are, at most, deemed

to be minimal risk by the IRB. They may not operate equipment that could, in the opinion of the IRB, pose significant physical risks (e.g., operating a magnetic resonance imaging (MRI) scanner or an experimental device).

As with any researcher involved in human subjects research, minors must complete the required CITI Human Subjects training education in the protection of human research participants, which is current within 5 years, or 3 years for clinical trials or DOD-sponsored projects. Minors may only interact with and collect data from human subjects under the supervision and responsibility of an adult researcher ("supervisor"). The supervisor or at least one other adult (other than the research subject) must be present in the research suite when a minor is collecting data from a subject. The supervisor must take responsibility for the study, train the minor in how to interact with human subjects and how to do the experiment, and be available for any questions as they arise. Minors may not administer informed consent, although they may be present during the informed consent process. It is recommended that the supervisor, after having obtained informed consent, introduce the participant and the minor and explain the nature of the study, before letting the minor take over to collect the data.

PIs that have minors interacting with and collecting data from human subjects must indicate on the personnel amendment application that the researcher is a minor.

iv. For researchers who are minors under 16 years of age, the IRB will consider each protocol on a case-by-case basis and may approve such minors to perform data analysis on human subjects, with subject consent.

b. description of human subjects involvement, including:

i. a description of how human subjects participate in the research, including a description of how they are recruited (e.g., through advertisements),

who they are (e.g., college students), whether they include vulnerable subjects, how many are anticipated (sample size), statistical rationale for sample size, and what the subjects will experience during the study session. This needs to be in accessible, clear English, 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 research subject would expect). Describe the types of stimuli that might be used, the tasks requested of the subjects, 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).

ii. 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:

(i) Identifiable data: Information that identifies the subjects are stored in the data set.

(ii) Coded data: Codes (e.g., numbers, letters, or symbols), rather than information that identifies the subjects, are stored in the data set. The investigator could readily ascertain the identity of the subjects though a "key" linking the information. For example, the PI may store the key to the code in their lab, separately from the coded data, e.g., in a locked cabinet, or in a separate encrypted, password protected file.

(iii) De-identified data: Data where subject identifiers were initially collected and have been removed, such as coded data where the link between the codes and the identifiable information has been broken, such that the investigator no longer has the ability to ascertain the identity of the subjects. Data may be de-identified by, for example, permanently destroying the key to the codes, or

a an agreement with the collaborator or vendor who collected the data that the key will not be shared, by contract or via a statement in a collaborator's IRB protocol that neither the key nor subject identifiers will be shared.

(iv) Anonymized data: Data is anonymized when the data has been de-identified and the code no longer exists. Anonymization is intended to prevent subject re-identification.

(v) Anonymous data: No identifying information was collected from the subjects. Examples include, paper-based surveys that do not collect any identifying information and online surveys that do not collect IP addresses. Note that with small subject 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.

Please see Caltech IRB *SOP 13: Anonymous, De-identified, & Coded Data* for the detailed process.

iii. copies of recruitment materials that will be used and, where informative, complete copies of questionnaires, thorough descriptions of samples of tasks and/or actual instructions, and samples of stimuli (e.g., provide complete description of, or the actual materials showing, what subjects will see on a computer while performing a certain task).

iv. a full description of potential risks to the subjects, 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.

(i) 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.

(ii) The IRB has determined that all functional MRI (MRI), Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulations (TDCS) studies are greater than minimal risk.

v. when the research is a collaboration with another institution, the Investigator should include 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.

c. as applicable, an indication that a Certificate of Confidentiality (COC) has been automatically granted as part of a NIH or other HSS award (all NIH-funded studies automatically obtain a COC), will be applied for in accordance with NIH provisions, or has been obtained from NIH.[5] 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 subject's identity.

[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.

d. evidence that all researchers 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 required 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.

e. identification of the funds used to support the study (sponsor, funding agency, gift or internal funding) and award number (if available).

f. a copy of the ICF, a copy of any information given to research subjects as part of the informed consent process, and a description of how informed consent will be obtained and documented, or alternatively, a justification for a waiver of informed consent. The online protocol submission system will generate an ICF from template information in most cases, but investigators need to carefully proofread and edit this system-generated ICF to ensure it is accurate, and conveys information in simple, clear English.

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

3. ELEMENTS OF THE INFORMED CONSENT FORM (ICF)

The ICF typically follows the template provided on Caltech's online submission system, which includes the following elements (many of these are specific sections that must be used with verbatim text and are provided in the template). Investigators are responsible for editing their ICF, and ensuring that all text is easily understandable, is generally well written, and provides a prospective subject 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 human subjects 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.

a. Research Description. The ICF must state that the study involves research, it must also give an explanation of the purpose(s) of the research, the expected

duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental. It is also important to state any requirements for inclusion or exclusion of subjects from the study.

b. Reasonably Foreseeable Risks. The ICF must provide a description of any reasonably foreseeable risks or discomforts to the subject. If applicable, the informed consent document should also state that the risks might not be fully known.

c. Benefits. The ICF must include a description of any benefits to the subject or to others that may reasonably be expected from the research. Based on the study, the ICF may state that there is no direct benefit to the subject, but that there is a broader benefit to science and society; such benefit needs to be briefly articulated in the ICF.

d. Alternative Procedures or Treatment. The ICF must include a disclosure of alternative procedures or courses of treatment, if any, that might be available to the subject. Often the ICF for basic research studies will state that an alternative is for the subject not to participate in the study.

e. Confidentiality of Record. The ICF must include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. It may be appropriate to include a statement that federal, state or local government agencies having authority over the research may have access to the records. For FDA regulated research, the ICF must also include a statement that there is a possibility that the FDA may inspect the record. If identifiable research data are kept for a limited time, this should be stated clearly (e.g., "the video recordings will be destroyed after one year").
If applicable, the ICF should also include a statement that a COC has been granted as part of a PHS award, has been applied for in accordance with NIH provisions, or has been obtained from NIH.

f. Compensation and Treatment for Injury. The ICF will include an explanation as to whether any compensation will be provided for participation. Additionally, the ICF should provide a separate explanation as to whether any medical treatments or compensation for injury are available if injury occurs. If medical treatments or related compensation are available, the ICF should describe

what is covered, whom to contact, and where further information may be obtained. The Caltech ICF template provides specific text for these sections that must be used, but which can be edited, based upon the location where treatment might be provided.

g. Contact Information. The ICF must provide an explanation of how and whom research subjects can contact for (1) answers to pertinent questions about the research and research subject's rights, (2) requests to withdraw, and (3) notification in the event of a research-related injury to the subject.

h. Voluntary Participation. The ICF must include a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. This is particularly important for any research involving clinical populations or a hospital setting, where it is critical to ensure that prospective participants understand the distinction between their clinical treatment as patients, and their voluntary participation as research subjects.

i. Collection of Identifiable Private Information or Identifiable Biospecimens: If researchers are collecting Identifiable Private Information[6] (IPI) or Identifiable Biospecimens[7] (IB) (refer to Section (II) for definitions the informed consent must include, as applicable:

    i. A statement that identifiers might be removed from the IPI or IB and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject; or

    ii. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies. If the information or biospecimens will not be used again, the investigator should provide a description of and timeline for destruction.

j. Support. All financial sponsors of the research must be disclosed in the ICF.

[6] *I*dentifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

[7] Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

k. Conflicts of Interest. When applicable, a disclosure statement by the investigator(s) involved in the research that they may have a potential or actual financial conflict of interest, along with any further explanation of the conflict, as deemed appropriate by the IRB.

l. Date of Approval/Expiration Date. All ICF must clearly state the date of the IRB approval and date of expiration. These dates may be left blank on the ICF template submitted to the IRB, but must be present on the IRB-approved ICF which will be used to consent subjects.

m. No Clinically Relevant Research Results. All ICF must include a statement that the study is for research purposes only and that no clinically relevant results will be collected nor will individual research results be disclosed to the subjects.

n. Number of Subjects: The ICF should provide the approximate number of subjects involved in the study.

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

o. Unforeseeable Risks. If applicable, the ICF should include a statement that the particular study or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable. It is recommended that investigators consider this addition for all studies that are more than minimal risk.

p. Termination of Participation by the PI. If applicable, the ICF should include any anticipated circumstances under which the subject's participation may be terminated by the PI without the subject's consent.

q. Additional Costs. If applicable, the ICF should include any additional costs to the subject that may result from participation in the research (such as travel costs).

r. Consequences of Subject's Withdrawal. If applicable, the ICF may need a statement reflecting the consequences of the subject's decision to withdraw from the research and procedures for safe and orderly termination of the participation of the subject.

s. Significant New Findings. If any significant new findings may arise during the course of the research which could relate to the subject's willingness to continue

participation, a statement that these findings will be provided to the subject and a description of the method of dissemination.

t. California Experimental Subject's Bill of Rights. For medical experiments and other experiments where the IRB deems it appropriate, prior to consent, subjects must be provided with an Experimental Subject's Bill of Rights in accordance with California Health & Safety Code § 24172. This is typically generated automatically as a section of the ICF by the online IRB system when investigators submit their protocols.

u. Incidental Findings: If applicable, include a statement as to how incidental findings will be handled. (See Incidental Findings V(I)(8) and *SOP 8: Incidental Findings*)

v. HIPAA Authorization: If applicable, a written authorization to use identifiable health information for research purposes in accordance with the Health Insurance Portability and Accountability Act (HIPAA) should be included in the informed consent document or a separate HIPAA Authorization Document.

w. Photographing and Recording: If applicable and deemed appropriate by the IRB, the ICF should include a statement that the subject will be photographed or audio or video recorded and whether or not the subject will be identifiable. The ICF should also include where such photographs or recordings will be kept, and the planned duration of retention. It is often appropriate to have the subject initial next to the relevant section of the ICF to indicate their understanding of such procedures.

x. Physical Contact: If applicable, and the research requires any physical contact with subjects, the nature of the contact needs to be disclosed in the protocol and the ICF. (See Studies Involving Physical Contact with Subject, V(I)(5) and *SOP 6: Physical Contact with Subjects*)

y. Fasting: As applicable, if a protocol requires the subject fast for any length of time prior to completing the written informed consent process, the investigator must receive general consent (see Documenting Informed Consent, V(A)(4)(d) and *SOP 3: Fasting in Human Subjects Research*) from the subject before the subject begins to fast. The ICF for the study must include a complete description of the fasting requirements.

z. Future Contact to Continue Data Collection: If applicable, the ICF should include a request for consent from the subject to be contacted in the future:

i. to obtain additional information,

ii. to arrange to collect additional data (e.g., another visit to the lab, or a questionnaire to fill out on the internet), or

iii. to request participation in other research studies at Caltech by the same or different researchers.

It is important to identify what contact information will be preserved (name, phone, email, etc.), where it will be stored, by whom, for what length of time and, as applicable, state that this contact information may be made available to and they may be contacted by other researchers at Caltech. It is often appropriate to have the subject initial to indicate their understanding of such future contact.

aa. Data Sharing: If applicable, the ICF should include information about any data sharing, the purpose of the data sharing, and whether the subject's identity will be ascertainable. If specific data repositories are contemplated, they should be included by name. It is strongly recommended that PIs include a data sharing plan in their protocols whenever feasible. For de-identified generic data sharing, template text should be considered.

bb. Commercial Use: If applicable, the informed consent document should state that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether or not the subject would share in such profit.

cc. Biospecimens: For research involving biospecimens, the informed consent shall include whether the research will (if known) or might include whole genome sequencing.

dd. BROAD CONSENT: If the study will require the storage, maintenance, and secondary research use of *identifiable* private information or *identifiable* biospecimens (collected for either research studies other than the proposed research or non-research purposes), researchers can elect to obtain "Broad Consent". The elements of a Broad Consent must include:

Elements b, c, e, h, and, if applicable, aa and bb, above as well as:

1. A general description of the types of research that might be conducted with the identifiable private information or identifiable biospecimens
2. A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens.
3. A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (can be indefinite) and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (can be indefinite.)
4. Unless the subject will be provided details about specific research studies, the Broad Consent must include a statement that the subject will not be informed about the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens. The subject must be told that this includes not knowing the purposes of the research, and that, their Broad Consent, includes consent to a research study that they might otherwise have chosen not to consent to.
5. Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, the Broad Consent should include a statement that such results may not be disclosed to the subject
6. An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

See Section (I)(1) for a discussion of addition informed consent requirements for research involving minors.

4. DOCUMENTING INFORMED CONSENT

Unless otherwise approved by the IRB, informed consent shall be documented by the use of a written IRB approved ICF and signed (including in an electronic format) by the subject or the subject's legally authorized representative. The ICF should be provided in advance of obtaining the signature in order to provide the subject 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.

If the IRB approves the investigator to obtain consent orally, the investigator must prepare a written summary of the procedures to review with the subject or his or legal representative as well as prepare a short written form for the subject 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 for some or all of the subjects if it finds any of the following:

a. 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 subject (or legally authorized representative) should be asked if the subject wants documentation linking the subject's research, and the subject's decision will govern; or
b. The research presents no more than minimal risk of harm to the subject and involves no procedures for which written consent is normally required outside of the research context; or
c. If the subject (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 subject, and provided that there is an appropriate alternative mechanism for documenting that informed consent was obtained.
d. If a protocol requires the subject 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 subject before the subject begins to fast. (See *SOP 3: Fasting in Human Subjects Research*)

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

i. 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.
ii. During recruitment, subjects 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 subject with a written statement regarding the research.

5. APPLICATION FOR ALTERATION OR WAIVER OF AN INFORMED CONSENT DOCUMENT

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.

a. Alteration

The IRB may not omit or alter the general requirements for informed consent, which include prospectively seeking consent from the subject (or the legally authorized representative), in language understandable to the subject, and providing the subject with key information to help the subject 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:

i. 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

ii. The research involves no more than minimal risk to the subjects; the research could not practicably be carried out without the waiver or alteration[8], the waiver or alteration will not adversely affect the rights and welfare of the subjects, and whenever appropriate, the subjects will be provided with additional pertinent information after participation.

b. Waiver

The IRB may waive the requirement to obtain informed consent for research provided that the IRB satisfies either (i) or (ii), under section a. Alteration, above.

In cases where the IRB approves a protocol with a waiver or alteration of informed consent, it may require the investigators to provide subjects with a written statement regarding the research and a statement regarding 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.

6. PROTOCOL CLASSIFICATION BY THE IRB

The IRB Chair may determine whether a protocol qualifies as not being human subjects research (in which case, no IRB involvement is needed). The IRB Chair, sometimes in consultation with other IRB members, will determine whether the research described in the protocol qualifies as exempt, or for expedited review. The IRB Chair, in consultation with the Institutional Official or member(s) 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 Institutional Official,

[8] 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.

will also determine whether a protocol can be approved on the basis of review by another Institution's IRB (e.g., "reliance" such as when a clinical trial is conducted entirely at a hospital and has been reviewed and approved by the IRB of that hospital).

7. PROTOCOL REVIEW BY THE IRB

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

a. determine whether the risk to human subjects is minimized (through using procedures consistent with sound research design with minimal unnecessary exposure to risk and, to the extent possible, using procedures already being performed on the subject for diagnostic or treatment purposes);
b. 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;
c. determine whether selection of the subjects is equitable and justified for the particular experiment being conducted;
d. determine whether the informed consent itself meets the criteria specified in this Policy;
e. 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;
f. determine whether the investigators have a method for appropriately documenting the informed consent;
g. determine whether there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
h. determine whether the protocol has adequate provisions for monitoring data collected to ensure the safety of subjects;
i. determine whether some or all of the subjects are likely to be vulnerable to coercion or undue influence (for example children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons, students, lab members, and/or acquaintances of persons in the lab). Should subjects be vulnerable, the IRB shall determine whether additional

safeguards have been included in the study to protect the rights and welfare of these subjects; and

j. 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.

8. APPROVAL

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 (for instance, in order to activate linked grants), but require further approvals for the research to begin (for instance, when conducting on-campus research during the COVID pandemic). 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.

9. NOTICE

After the IRB has made a decision on whether to approve, disapprove, require modification of the protocol in order to secure approval, or defer the application, it will notify the PI and the Institutional Official 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, described below. 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.

10. PROTOCOL AMENDMENTS

Protocol amendments (i.e., modifications to approved protocols) shall be submitted before any deviations from the approved protocol are made. The modifications may be eligible for expedited review, as described below in Section V(C) or full review, as described above.

B. EXEMPT RESEARCH

In accordance with federal regulations, certain research involving human subjects is exempt from IRB review. If a PI believes their research qualifies for exemption, they should submit an Initial Query through the IRB protocol application system, describing the project and identifying the likely basis for the exemption.

If research qualifies as exempt, it will be reviewed by the IRB Chair in consultation with other members of the IRB, as needed. Upon this determination, the IRB Administrator will inform the PI that continuing IRB review and approval is not required but that an appropriate notice and/or ICF may still be required by Caltech to fulfill obligations outside of the purview of the IRB. Exempt protocols do not require annual review, but investigators are obligated to inform the IRB if their exempt protocol changes, in any significant way.

Certain categories of subjects 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 subject 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:

a. **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)).

b. **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 human subjects 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[9] 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))

c. **Exemption 3**: Research involving benign behavioral interventions[10] 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:

i. 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));

ii. 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)(ii)); or

[9] Limited IRB review is a process that is required only for certain exemptions, and does not require an IRB to consider all of 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.

[10] 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.

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 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)(iii))

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.

d. **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.

e. **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))

f. **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))

g. **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))

h. **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))

C. CONTINUING REVIEW

1. FREQUENCY

Except as provided, below, all 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 subjects or that subjects 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, as provided, below. 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 submitted to the Caltech IRB Administrator for our records, prior to work continuing at Caltech.

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 human subjects 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 human subjects activity under the protocol may not resume until the IRB has reviewed and approved the protocol.

2. INVESTIGATOR SUBMISSION

PIs must submit an Application for Continuing Review to the IRB, which is found online through access.caltech.edu - IRB Submission and Review Module, and consist of:

a. the approximate number of subjects enrolled in the past year. Investigators are also requested to state the total number of subjects enrolled in the study to date, in the annual progress summary box at the very beginning of the protocol renewal,
b. a summary of adverse events and any unanticipated problems involving risks to subjects or others, and any withdrawal of subjects from the research or complaints about the research since the last IRB review,
c. any relevant amendments or modifications to the research since the last review,
d. any relevant multi-center clinical trial reports,
e. any relevant reports from study data monitoring,
f. any relevant information (particularly information about risks associated with the research),
g. .any requested changes to the informed consent document

The IRB may also determine that additional information is necessary. Projects requiring such additional information include projects with unusual levels or types of risks to subjects. In addition, the IRB may inspect facilities where human subjects research takes place and where data and records are maintained, and may request more detailed information about the investigators' recordkeeping practices. The IRB may designate members to inspect research facilities, or may designate a third party to inspect.

3. APPROVAL

Continuing Review may be expedited as described below (Section (D)(3)).

All other Applications for Continuing Review will be reviewed by a subcommittee who will make a recommendation to the full IRB for approval, disapproval, requirement to make modifications to secure approval, or deferral. The subcommittee will be comprised of a subset of IRB members chosen by the Chair. After review, the IRB will vote on whether or not to approve, disapprove, require modifications to secure approval of, or defer the application for continuing review during a convened meeting.

4. NOTICE

The PI will be provided with notice of approval, disapproval, requirement for modifications to secure approval, or deferral of the Review application. In the event that modifications are

needed to secure approval, the IRB Administrator will contact the PI to convey the IRB requirements and help the PI submit the required modifications. As desired by the PI, in the event of disapproval or deferral, the IRB Administrator will contact the PI to assist the PI in preparing the application for re-submission.

D. EXPEDITED REVIEW

1. RESEARCH ELIGIBLE FOR 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 (for details, please see http://www.hhs.gov/ohrp/policy/expedited98.html). Expedited review cannot be used if the identification of the human subjects would reasonably place them at risk of liability or be damaging to the subjects in any way; or the research is classified. The following may qualify for expedited review:

a. 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 1)

b. 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 (Category 2[11]),

c. prospective collection of biological specimens by non-invasive means (Category 3),

d. collection of data through non-invasive procedures routinely employed in clinical practice, except for X-rays, microwaves or MRI (Category 4),

e. collection of materials that have been already previously produced for non-research purposes, such as materials used for medical treatment or diagnosis (Category 5),

[11] 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.

f. data from voice, digital, or image recordings made for research purposes, provided that the subjects are not identifiable (Category 6),

g. 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 7).

h. 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.

2. PROCEDURE FOR EXPEDITED REVIEW

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 (or protocol amendment) using the same criteria as would be used by the full IRB (either for new or continuing applications) and may either approve, require modification to, or refer the research to the full convened IRB for review.

The Chair will inform each PI and the full committee of all protocols approved through the Expedited Review process. The IRB will ratify the subcommittee's approval at the next IRB meeting, or subject the protocol to further review. Any member at the full committee meeting may request a detailed explanation of an expedited protocol approval to clarify any questions related to that approval.

3. EXPEDITED CONTINUING REVIEW

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:

a. 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,

b. 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).

c. 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,

d. no subjects have been enrolled and no additional risks have been identified, or

e. the remaining research activities are limited to data analysis.

E. REVIEW OF CLASSROOM STUDIES

Although classroom studies involving human subjects in undergraduate and graduate courses typically do not meet the regulatory definition of research (see Section II, above), 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 humans should submit a query to the IRB.

F. COOPERATIVE RESEARCH, RELIANCE ON ANOTHER IRB, AND SINGLE IRB REVIEW

Cooperative research projects are those 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 human subjects 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 human subjects 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 of 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 on another IRB or to implement joint IRB review may be made by the Chair, in consultation with the Institutional Official, 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, a full application, or a newly designed application specific for these type of agreements with all of 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 to 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 our 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.[12] Such

[12] 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

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.

G. APPLICATIONS AND PROPOSALS LACKING DEFINITE PLANS FOR INVOLVEMENT OF HUMAN SUBJECTS A.K.A "DELAYED ONSET OF RESEARCH" OR A "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 subjects 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 subjects remain to be selected; and projects in which human subjects' 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 human subjects 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 Institutional Official, or the IRB Administrator in consultation with the Institutional Official. The initial application for a "118 Determination" will require the Caltech PI to submit a Caltech IRB Initial Query application (or a newly designed application specific for these type of agreements) with all of 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 you consult with the IRB when drafting your proposal to verify that a "118 Determination" is appropriate for your study.

H. REVIEW OF FDA-REGULATED RESEARCH: RESEARCH ON DEVICES

All studies of investigational devices, unless exempt from the regulation, must have an Investigational Device Exemption (or its equivalent) approved by the IRB for Non-Significant Risk (NSR) devices, or from the IRB and FDA for Significant Risk (SR) devices before the study may begin.[13] 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 an investigation, and may not begin the investigation until the IDE is approved (21 C.F.R. § 812.20).

Before submitting an IDE for an investigator-led trial, the PI must submit and IRB application and include that an IDE is being requested. For use of a NSR device, a PI must submit an IRB application, with the PIs determination, to the IRB for review and approval. For use of a SR device, an IDE application to the FDA to use a significant risk device in an investigation, and may not begin the investigation until the IDE is approved (21 C.F.R. § 812.20).

The IRB can assist the investigator in preparing the necessary documentation for the IDE application. See Section (5)(H)(1)-(4) for additional information on risk determination.

Whether studies on medical devices involving human subjects may be conducted on campus or at JPL depends on the level of risk to the subjects. All studies involving FDA-regulated research must be done in accordance with all of the applicable regulations and Caltech policies described in this document.

1. RISK CLASSIFICATION FOR DEVICES

a. Significant Risk Devices: These devices pose serious risk to the health, safety, or welfare of a subject, and include, but are not limited to, implants, devices that support or sustain human life, and devices that are of substantial importance in diagnosing or treating disease. Significant risk devices must have an

[13] 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)).

Investigational Device Exemption (IDE), 510(k) premarket notification to the FDA, premarket approval (PMA), humanitarian device exemption (HDE), or similar approval approved by the FDA before a study may proceed.

b. Non-Significant Risk Devices: These devices are defined as investigational devices that do not meet the definition of a significant risk device. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. Examples include most daily-wear contact lenses and lens solutions, and some experimental non-invasive devices. . A non-significant risk device study requires only IRB approval prior to initiation of a clinical study. Sponsors of studies involving non-significant risk devices are not required to submit an IDE application to the FDA for approval. Submissions for non-significant device investigations are made directly to the IRB of each participating institution. Sponsors should present to the reviewing IRB an explanation why the device does not pose a significant risk. If the IRB disagrees and determines that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days [§812.150(b)(9)]. The FDA considers an investigation of a non-significant risk device to have an approved IDE when the IRB concurs with the non-significant risk determination and approves the study.

c. Exempt devices: These devices do not pose significant risk to subjects and are exempt from the requirements of 21 C.F.R. § 812.2(b).

Studies involving testing of a device for consumer preference, testing of a device modification, testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data, and does not put subjects at risk may be exempt. However, studies of a medical device which has already been approved by the FDA where the device is to be used or investigated in accordance with the indications in the FDA approved labeling are exempt; however studies of an FDA approved device for a new, unapproved use are not exempt.

Diagnostic device studies may be exempt as long as the testing is non-invasive, does not require an invasive sampling procedure that presents a significant risk, does not by design or intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure (21 C.F.R. § 812.2(c)).

2. DETERMINING THE RISK CLASSIFICATION

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

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

The IRB requires that all devices used in a study are listed in the protocol. If the PI considers an investigational device to be a Non-Significant Risk or an exempt device, the PI will state their initial recommendation that the device is exempt or Non-Significant Risk, and provide a risk assessment and rationale as to why the IRB should consider the device exempt or Non-Significant Risk. Information provided should include a description of the device, a risk assessment, reports of prior investigations with the device (if any), the proposed investigational plan, the subject selection criteria, and rationale for why the study should be considered a non-significant risk or exempt device.

If the PI considers the device to be a Non-significant risk or exempt device, the protocol shall include an explanation of this determination and information that will be helpful for the IRB to determine the risk. In addition to the requirements of every protocol submission, a protocol submission for a study involving an investigational device should include:

a. description of the device,
b. the FDA classification of the device, if applicable, i.e., Class I (lowest risk), II, or III (highest risk),
c. reports of prior investigations using the device,
d. risk assessment,
e. rationale for why the study should be considered exempt or non-significant risk, and
f. any other substantiation information.

If the PI considers the device to be a non-significant risk or exempt device, and the IRB disagrees or cannot determine the risk, the PI or the IRB may ask the FDA to make or assist with a risk determination. If the PI considers the device to be a non-significant risk or exempt device, the IRB may agree, but in case of disagreement, the IRB has the discretion to consider the device as a significant risk device.

3. STUDIES ON SIGNIFICANT RISK DEVICES

Similar to studies involving drugs and biologics, studies of significant risk 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.

4. STUDIES ON NON-SIGNIFICANT RISK DEVICES

If the IRB makes the determination that the study involves a non-significant risk device, the IRB may approve the study.

The IRB may review protocols for studies on non-significant risk 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.

I. SPECIAL CIRCUMSTANCES AND VULNERABLE POPULATIONS

Research involving vulnerable,[14] medically complex[15] 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.

1. MINORS (CHILDREN)

Research involving non-neonate subjects, 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 researchers who will be collecting data must meet requirements provided in Caltech's Staff Personnel Memoranda on Minors (PM) and abide by Caltech's Standards 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. For example, there may be a requirement to have an additional adult researcher present whenever collecting data from a minor.

Research involving minor subjects may be exempt from IRB review, as described above in sections V(D), and V(E)) of this policy. As described above in section V(E)(b.), educational tests, surveys, interviews and observation of public behavior research with minors may be exempt ONLY when the research involves observations of the subjects' public behavior AND the researcher is NOT participating in the activities being observed.

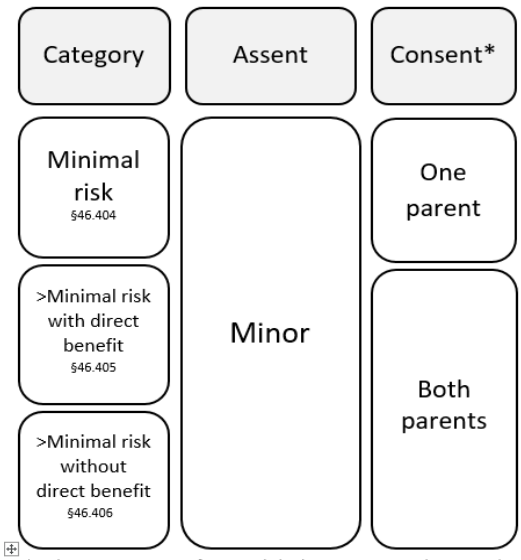
If the research on minors is not exempt from IRB review, the research will be reviewed by the IRB to ensure that all of the standard Caltech requirements for review and approval are met, as

[14] Vulnerable populations is defined as subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

[15] Medically complex subjects may include pregnant women and other conditions with complex care needs.

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 subject 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 subjects are not capable of providing assent, the IRB may approve research where the assent of some or all of the subjects is not required.



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

For research that involves only minimal risk, or a small increase over minimal risk where the prospect of direct benefit to the subject 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 subjects to justify the risk, but where the research is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition, 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 subject population, e.g., neglected or abused children, it may waive the consent requirements, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. If the research meets these criteria, the IRB may elect to approve the research. If the research meets the criteria described in Section V(C), it may be approved in an expedited review.

2. NEONATES, PREGNANT WOMENAND FETUSES

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

3. 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.

4. 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 by the entire IRB to ensure that all of the standard Caltech requirements for review and approval are met as well as to ensure that the research is compliant with all federal regulations.

5. STUDIES INVOLVING PHYSICAL CONTACT WITH SUBJECTS

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. (See *SOP 6: Physical Contact with Human Subjects*) In general, for the safety and security of both the subject and the investigators, PIs 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. It is recommended that when physical contact with a subject is expected, there are two attentive investigators in the room. Exceptions to this policy will be reviewed on a case by case basis.

VI. INVESTIGATOR RESPONSIBILITIES,NONCOMPLIANCE, PROTOCOL DEVIATIONS, AND VIOLATIONS

A. 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 human subjects, 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 human subjects 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.

A Caltech PI is responsible for submissions of protocols and responding to IRB requests. Failure to submit protocols timely 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 subjects (resulting from unanticipated problems and other events).

B. NONCOMPLIANCE

Should a PI 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(s) and determine whether it is appropriate to suspend or terminate the research.

OHRP may perform compliance oversight evaluations of Caltech 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 human subjects in an investigation.

C. 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 (including amendments) or consent document.

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

a. deviations that may affect the risk/benefit analysis of a study,

b. deviations that may affect the rights, health, and/or welfare of a subject,

c. deviations that may affect the safety and/or privacy of a subject,

d. deviations that may affect a subject'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 or 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.

D. 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.

E. 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):

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

VII. UNANTICIPATED PROBLEMS AND OTHER EVENTS

A. DEFINITIONS

An Unanticipated Problem is an event that is unexpected in light of 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.

B. 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 as well. The IRB Chair will notify the Institutional Official and keep the Institutional Official apprised of any developments.

1. 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 Institutional Official shall be notified of both serious and non-serious events as soon as possible.

2. 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 Institutional Official, the PI, and OHRP, FDA, and the sponsor (as applicable) when the following apply:

a. the event is a reportable event under the OHRP or FDA regulations,
b. the event is serious and unanticipated,
c. the event is not serious and anticipated, but the event is occurring at a frequency or with greater severity than expected,
d. the event involves risk to the subjects or others,
e. the event has resulted in suspension or termination of IRB approval, or
f. 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.

VIII. REPORTING TO OHRP AND FDA

A. 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.

B. NONCOMPLIANCE, PROTOCOL DEVIATIONS, AND VIOLATIONS

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

C. SUSPENSIONS OR TERMINATIONS OF IRB APPROVAL

All suspensions or terminations of IRB approval shall be promptly reported by the Institutional Official as described above in Section VII(B).

IX. IRB RECORDKEEPING

A. 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.

B. IRB POLICY

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

C. DOCUMENTATION OF IRB ACTIVITIES

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

a. records of all Applications for Approval of Human Subjects Research, including research proposals reviewed, scientific evaluations (if any), approved informed consent documents that have been reviewed by the IRB,

b. records of all continuing review summaries and other progress report documentation submitted by investigators,

c. reports of any injuries to subjects, adverse or other events,

d. 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.

e. 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,

f. documentation of risk assessment of any study devices, noting its decision of significant risk, non-significant risk, or exempt in the meeting minutes,

g. records of all correspondence between the IRB and the investigators,

h. 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

i. 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).