UNANTICIPATED PROBLEMS & ADVERSE EVENT REPORTING	SOP 8.1.01

1. Purpose & Policy

The purpose of this SOP is to provide guidelines for prompt investigator reporting of Unanticipated Problems or Adverse Events to the Institutional Review Board (IRB) and to ensure that such problems and/or events are defined, recorded, reported, and evaluated as required by the IRB. IRB Policy *Section 8.*

2. General Information

A. Regulatory guidance provided in 45 CFR 46.108(a)(4) relating to the Office for Human Research Protections (OHRP) and 21 CFR 56.108(b) relating to the Food and Drug Administration (FDA) requires the IRB to have written procedures for ensuring prompt reporting to the IRB, appropriate Caltech officials, and applicable regulatory agencies of any Unanticipated Problems or Adverse Events involving risk to study participants or others.

Adverse Events are often physical in nature, but attention must be paid to psychological harm (e.g., depression, thoughts of suicide), threats to privacy, and participant safety as well. An event is considered serious and must be reported when the participant experiences an unusually strong response, recurring problems, and/or death.

Everyone, including investigators, members of the Caltech community, study participants, etc., are encouraged to report events to the IRB, Institutional Official (IO), or the Caltech Hotline. The IRB or the IRB Chair will notify the IO and keep the IO apprised of any reported events.

B. Definitions

Adverse Event:

a. Per the OHRP, an Adverse Event is any untoward or unfavorable medical occurrence in a study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

Adverse Events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

b. Per the FDA, an Adverse Event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event:

a. Per the OHRP, a Serious Adverse Event is any Adverse Event that:

   i. results in death;

   ii. is life-threatening (places the participant at immediate risk of death from the event as it occurred);

   iii. results in inpatient hospitalization or prolongation of existing hospitalization;

   iv. results in a persistent or significant disability/incapacity;

   v. results in a congenital anomaly/birth defect; or

   vi. based upon appropriate medical judgement, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

b. Per the FDA, a Serious Adverse Event is an event or reaction that, in the view of either the investigator or sponsor, resulting in any of the following outcomes:

   i. death;

   ii. a life-threatening Adverse Event;

   iii. in-patient hospitalization or prolongation of existing hospitalization;

   iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

   v. a congenital anomaly or birth defect.

Unanticipated or Unexpected Adverse Event:

a. Per the OHRP, an Unanticipated or Unexpected Adverse Event is any Adverse Event occurring in one or more participants in a research protocol, the nature, severity, or frequency of which is not consistent with either:

    i. the known or foreseeable risk of Adverse Events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document; and (b) other relevant sources of information, such as product labeling and package inserts; or

    ii. the expected natural progression of any underlying disease, disorder, or condition of the participant(s) experiencing the Adverse Event and the participant's predisposing risk factor profile for the Adverse Event.

b. Per the FDA, an Unanticipated or Unexpected Adverse Event is an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current Investigational New Drug (IND) application.

Unanticipated Problem:

a. Per the OHRP, an Unanticipated Problem is any incident, experience, or outcome that meets all of the following criteria:

    i. unexpected (in terms of nature, severity, and frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and

    ii. related or possibly related to a participant's participation in the research; and

    iii. suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

b. Per the FDA, an Unanticipated Problem holds the same definition as Adverse Event, i.e., any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse Reaction: Per the FDA, any Adverse Event caused by a drug.

Event: Per IRB Policy *Section 8.1*, the term "event" refers to Adverse Events, Serious Adverse Events, Unanticipated or Unexpected Adverse Events, and Unanticipated Problems, as well as other incidents, experiences or outcomes that may be related to an Unanticipated Problem.

3. Training Requirements

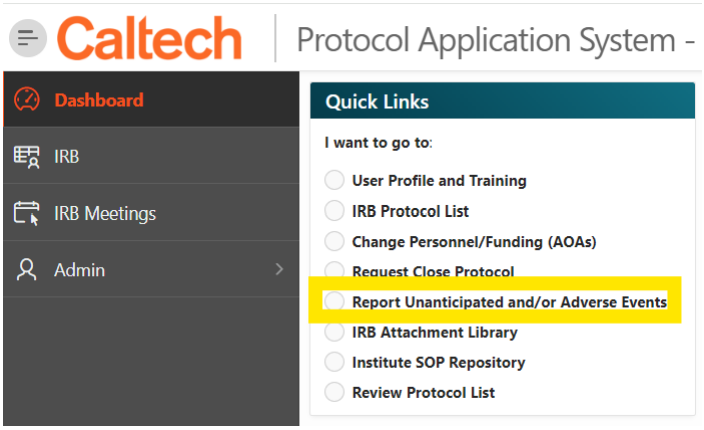
Other than the normally required and study specific training for all human subjects research, there are no additional specific training requirements associated with unanticipated problems and adverse events; however, investigators should carefully read and follow this guidance.

4. Procedure

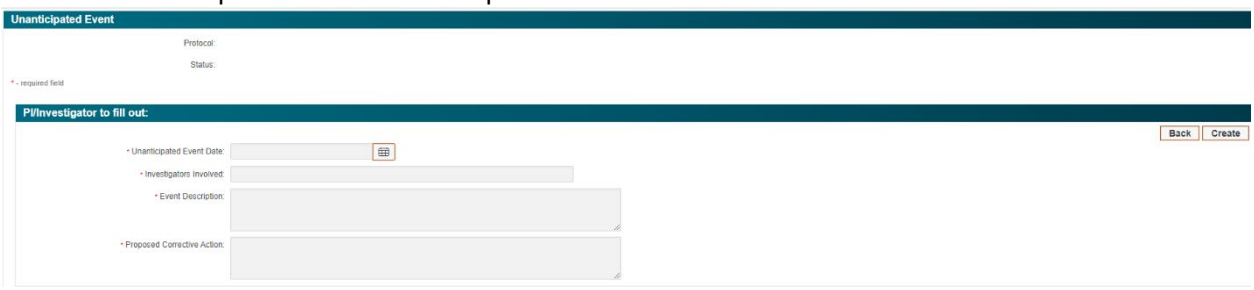
A. Principal Investigator (PI) Responsibilities

The PI must report all suspected events to the IRB through the IRB Protocol Application System (PAS).

1. To locate event reporting, navigate to the PAS Dashboard. Under *Quick Links*, select *Report Unanticipated and/or Adverse Events*.



2. The following screen includes a list of the PI's protocols. Click on the protocol number to open the report that must be completed and submitted.



3. If an event is reported directly to the IRB or IO, the IRB Administrator or IRB Chair can enter the initial report into PAS on behalf of the PI. If reported by someone other than the PI, the PI will be notified of any reported events.

   Serious Adverse Events must be reported to the IRB within twenty-four (24) hours of the researcher or PI becoming aware of the event.

   Any other Unanticipated Problem or Adverse Event should be reported to the IRB within five (5) calendar days of the researcher or PI becoming aware of the event.

   The initial report shall include (#1-4 are already provided in PAS):

   1) the name of the PI,
   2) the name of the research project,
   3) the grant title, grant number, and funding agency,
   4) the IRB protocol number,
   5) the date of the event,
   6) the nature of the event, and
   7) any proposed corrective actions.

Upon receipt of the report, the IRB will notify the IO of both serious and non-serious events as soon as possible. The IRB may request that the PI provide additional or more detailed information.

B. IRB Responsibilities

The IRB Chair, in consultation with the IO, will make an initial determination as to whether the event is serious or not serious, and may ask the PI 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 determined to be serious, a subcommittee shall be formed to meet as soon as feasible, ideally within forty-eight (48) hours of the IRB's receipt of the initial report.

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

In determining 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 the 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.

If the subcommittee determines that an event is unrelated to the research, the research will be reinstated and the event, if reportable, will be reported to the OHRP or FDA within thirty (30) days of the research being reinstated.

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

1) the event is a reportable event under the OHRP or FDA regulations,
2) the event is serious and unanticipated,
3) the event is not serious and anticipated, but the event is occurring at a frequency or with greater severity than expected,

4) the event involves risks to the participants or others,

5) the event has resulted in suspension or termination of IRB approval, or

6) 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.

5. Informed Consent (IC)

PAS automatically includes the language below in the informed consent document so study participants can report research-related injuries directly to the PI and/or IRB.

Offer to Answer Questions and Research Injury Notification:

*The principal investigators or their research associates have offered to answer any and all questions regarding your participation in this research study. If you have any further questions or in the event of a research-related injury, you can contact the principal investigator at 626-395-****, or the Caltech Institutional Review Board Administrator at (626)395- 8448 or at irb@caltech.edu.*

After review of an Unanticipated Problem or Adverse Event, the IRB may require that the language in the informed consent document be updated.