

Public Health Division

Reports of Unanticipated Problems and Adverse Events

Any unanticipated problems (UAP) or adverse events (AE) involving risks to research subjects as a result of their participation in the study must be promptly reported to the Public Health Institutional Review Board (PH IRB) for review. More information can be found in the OHRP guidance:

- [Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#), and
- [Reporting Incidents to OHRP \(2022\)](#)

Definitions:

- **Adverse event:** any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease temporally associated with the individual's participation in the research, whether or not considered related to the subject's participation in the research. This includes both physical and psychological harms and occurs most commonly in the context of biomedical research.
- **External Adverse Event:** From the perspective of one particular institution engaged in a multicenter clinical trial, those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.
- **Internal Adverse Event:** From the perspective of one particular institution engaged in a multicenter clinical trial, those adverse events experienced by subjects enrolled by the investigators at that institution. In the context of a single-center clinical trial, all AEs would be considered internal.
- **Unanticipated Problem:** Any incident, experience, or outcome that meets *all the following criteria*:
 1. Unexpected given the nature of the research procedures and the subject population being studied;
 2. Related or possibly related to an individual's participation in the research; and
 3. Suggests that the research may place subjects or others at increased risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Investigator Responsibility:

The Principal Investigator must:

- Using the PH IRB Unanticipated Problem/Adverse Event Report form, analyze and review the particular incident, experience, or outcome to determine if it is an adverse event, an adverse event that is reportable as an unanticipated problem, or an unanticipated problem.
- Submit the form to the PH IRB Administrator, including the Chair and Vice Chair on the e-mail correspondence, within the time frames specified below.

What is Reportable and When to Report:

If unsure, Principal Investigator's should always consult with the PH IRB Administrator as soon as possible regarding the specific occurrence and whether or not it should be formally reported to the IRB. In assessing the situation, the research team should review the provided guidelines and the Unanticipated Problem Analysis Chart found on the last pages of the PH IRB Unanticipated Problem/Adverse Event Report form as it will assist in deciphering the occurrence as either an unanticipated problem or an adverse event.

Formal reports using the PH IRB Unanticipated Problem/Adverse Event Report form must be made

by the Investigator to the PH IRB within the following time frames:

- Fatal or potentially life-threatening unexpected problems must be reported to the PH IRB within five (5) working days after the Investigator learns of the event. If it is determined that a change is required to the protocol or consent form due to the event(s), revisions must be made promptly for submission to the PH IRB for review.
- All other unexpected problems must be reported to the IRB within fifteen (15) working days of the Investigator learning of the event. Again, if it is determined that a change is required to the protocol or consent form due to the event(s), revisions must be made promptly for submission to the PH IRB for review.

Further, a brief summary of such events must be submitted with the Continuing Review Questionnaire or Annual Check-in Form at the time of the yearly update with the PH IRB. The PH IRB may also request a report or additional information from the Investigator at any time it deems necessary.

PH IRB Review of Submitted Reports:

Upon receipt of the report, the PH IRB Administrator will conduct an extensive preliminary review and assessment to ensure the description of the occurrence corresponds with the context of the report, including what the Principal Investigator has distinguished it as. Already taken actions and/or proposed changes brought forward by the Investigator as a result of the event will be analyzed by the PH IRB using federal guidance to determine whether or not further action or revisions should take place. The report will be sent to the PH IRB Chair and/or Vice-Chair by e-mail along with a detailed summary, a recommendation for next steps, and a draft determination memo. Either the Chair, Vice-Chair, or a designated PH IRB Board member of their choosing, will then provide a formal review. Any minor modifications to the protocol or supplemental study documentation that result due to the event, may be reviewed and approved in accordance with expedited procedures by the reviewer. If any resulting modifications are more-than minor in nature however, they must be brought forward to the Full Board. E-mail review and approval will be permissible due to the quick turnaround required for such situations. Additionally, if the PH IRB Administrator is not present to provide the pre-review, that step may be bypassed.

Notification of Review and Determination:

Once approved, a copy of the final determination memo will be sent to the Principal Investigator explaining the details of the PH IRB's review, whether or not proposed changes have been approved or if further changes are needed, who else, if anyone will be notified, and in some cases whether or not the study is suspended or terminated. The Full Board will be notified of the report, actions taken as a result of it, and the PH IRB determination, either at the next scheduled PH IRB meeting or promptly via e-mail. If at that time additional actions are requested the research team will be notified.

- Adverse Events: If found to be an adverse event, the PH IRB will review the study protocol to see if a monitoring entity has been designated. If so, the research team will be required to notify the entity so they may too review, as they may subsequently find that per their review it does in fact qualify as an unanticipated problem and thus further reports must be made.
- Unanticipated Problems: If found to be an unanticipated problem, the PH IRB will notify the Office for Human Research Protections (OHRP) and the supporting HHS Agency head as is required per federal regulations. The reporting requirements in 45 CFR 46 do not specify a time frame, except to say it must be done in a "prompt" manner. In some instances, it may be

appropriate for the PH IRB to submit an initial report to OHRP, indicating that a follow-up or final report will follow by a specific date, or when a final determination has been made.

- [Office for Human Research Protections' Incident Report Form](#)

Note, proposed modifications that are disapproved by the PH IRB may be appealed by the Principal Investigator and the PH IRB may require additional information be submitted by the Investigator, Data Safety Monitoring Board, the study sponsor, or the study coordinating center on any event or unanticipated problem at any time.

Applicable Regulations:

45 CFR 46.108

21 CFR 56.108(b)