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.

Definitions:

- Adverse event: any untoward or unfavorable medical occurrence in a human subject, although not necessarily unexpected 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: Adverse events experienced by subjects enrolled by investigators at other institutions engaged in the relevant PH IRB approved clinical trial.
- Internal Adverse Event: Adverse events experienced by subjects enrolled by the investigators at the institution for which the study came to the PH IRB for review.
- 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 Coordinator 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 Coordinator 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 at the time of the subsequent continuing review with the PH IRB and the PH IRB may 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 Coordinator will review and 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 and the Coordinator will use federal guidance to determine whether or not further action or revisions should take place. The PH IRB Coordinator will then send the report to the IRB Chair or Vice-Chair by e-mail along with a determination recommendation. Either the Chair, Vice-Chair, or a designated PH IRB Board member will then provide a subsequent review. Any minor modifications 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.

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 report, actions taken as a result of it, and the PH IRB determination memo will too be discussed in person by the Board at the next scheduled Full Board review and 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.

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 46.103(5)
21 CFR 56.108(b)