Guidance for Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

Unanticipated Problems

In general, DHHS OHRP considers an *unanticipated problem involving risks to participants or others* as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the HSC-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research placed subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The HSC requires PIs to report an unanticipated problem **within five days** of becoming aware of the problem. Examples of unanticipated problems include:

- An actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, side effects, etc.).
- An unforeseen development that potentially increases the likelihood of harm to participants or others in the future.
- A problem involving data collection, data storage, privacy, or confidentiality;
- A participant complaint about approved research procedures.
- New information about a research study that indicates a possible change in the research risks to participants (sources may include a publication in the literature, interim findings, safety information released by the sponsor or regulatory agency, or safety/medical monitoring report).
- Deviations from an approved research protocol initiated without HSC review and approval to eliminate apparent immediate hazards to the participants.
- Incarceration of a subject.
- A sponsor-imposed suspension of a protocol due to possible increased risk.

However, if a protocol deviation or unanticipated problem meets any of the following criteria, the protocol deviation or unanticipated problem is **considered serious and must be reported to the HSC within 24 hours**:

1. Was unanticipated and unexpectedly serious (in terms of nature, severity, or frequency) or life-threatening.
2. Resulted in hospitalization or prolongation of hospitalization or death.
3. Resulted in a persistent or significant disability/ incapacity.
4. Resulted in suspicions that exposure to an investigational drug/device prior to conception or during pregnancy resulted in an adverse outcome (congenital anomaly/birth defect) to a child.

5. Based on appropriate medical judgment, the protocol deviation or unanticipated problem may jeopardize the subject's health and may require medical/surgical intervention to prevent one of the other outcomes listed in 1-4 above.

Unanticipated Problems Report Template

Unanticipated problems that meet the criteria above will generally warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive change that might need to be considered include:

- changes to the research protocol to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks;
- modification of the continuing review schedule;
- notification of current subjects when such information may related to subjects' willingness to continue;
- requirement for the investigator to re-consent current participants;
- provision of additional information about newly recognized risks to previously enrolled subjects;
- termination of the protocol with consideration for health and wellbeing of currently enrolled subjects;
- reporting or referral to federal agency and/or sponsoring organization.

Upon completing its review of the Unanticipated Problem Report, the HSC will inform the PI in writing of its determination and describe any corrective actions required.

Adverse Events

In general DHHS OHRP considers an *adverse event* to be any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical effect or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject'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. Not all adverse events are unanticipated problems. Only those adverse events that meet all three criteria for unanticipated problem need to be reported.