8 Reportable Events, Non-Reportable Events and Unanticipated Problems Involving Risks to Subjects or Others

CMU complies with DHHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others to the IRB, institutional officials, and relevant federal agencies and departments.

The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the auspices of CMU.

8.1 Definitions

UPIRSO - Unanticipated problems involving risk to subjects or others –Any incident, experience, outcome, or new information that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or 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 subject population being studied;
2. related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unexpected – The incident, experience, or outcome is not expected (in terms of nature, severity, or frequency), given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent documents, and the characteristics of the subject population being studied.

Unanticipated adverse device effect - 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 (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects [See 21 CFR 812.150(a)].

Related – There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event – Any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal

laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

Note: Only a fraction of Adverse Events are UPIRSOs and not all UPIRSOs are Adverse Events.

8.2 Reportable Event Procedures

8.2.1 Reporting by Investigator

Investigators must promptly (according to reporting schedule in 8.2.2) report the following problems to the IRB:

1. Adverse events involving direct harm to participants which, in the opinion of the principal investigator, meet the criteria for an unanticipated problem involving risk to subjects or others.
2. An unanticipated event related to the research that exposes participants to risk but that does not involve direct harm to participants.
3. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to risk.
4. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
   Note: CMU will not conduct research on drugs that require an IND
5. New information that indicates a change to the risks or potential benefits of the research. For example,
   a. An interim analysis or safety-monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
   b. A paper is published from another study that shows that the risks or potential benefits of your research might be different than initially presented to the IRB.
   c. A breach of confidentiality.
   d. Incarceration of a participant in a protocol not approved to enroll prisoners.
   e. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.
   f. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
   g. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
   h. Sponsor imposed suspension for risk.
   i. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
   j. Unanticipated adverse device effect.
   k. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

8.2.2 Submission of Reports by Investigator

Investigators must report possible unanticipated problems to the IRB promptly (according to reporting schedule in 8.2.2).

If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) days of receiving notice of the event.

Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days or as soon as practicable from the date of the event or from the date the investigator is notified of the event.

Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.

Investigators or the study team must report possible unanticipated problems to the HRPP Office in writing using the **Adverse/Reportable Event Form**. The written report should contain all of the following:

1. Detailed information about the possible unanticipated problems, including relevant dates.
2. Any corrective action, planned or already taken, to ensure that the possible unanticipated problems is corrected and will not occur again.
3. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.
4. Any other relevant information.
5. Any other information requested by the HRPP Office.
6. A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded to the IRB Chair if the IRB staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the DRC will notify the PI on the study when appropriate.

8.2.3 Processing Reports of Possible Unanticipated Problems

8.2.3.1 Review by IRB Staff and Chair

1. Upon receipt of an Adverse/Reportable Event form from a PI, the IRB support staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will contact the investigator or the designated contact person to obtain additional information. Corrections are documented in the IRB file, indicating the date, the person spoken with, and the IRB staff making the correction.
2. The IRB chairperson and/or other experienced IRB member(s), or compliance office staff designated by the IRB chairperson receives and reviews the report of the event(s) considered to be an unanticipated problem. The IRB chairperson (or designee) will make the final determination as to whether the event is to be regarded as an unanticipated problem.

3. Based on the information received from the investigator, the IRB Chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee must be reported to a meeting of the convened IRB.
4. The IRB or the IRB chairperson (or designee) has authority to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any Adverse Event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.
5. The reviewer will assess whether a reported event:
   a. Was anticipated or unanticipated
   b. If participants or others were harmed or at increased risk of harm.
6. If the reviewer considers that the problem was foreseen (was expected):
   a. the reviewer indicates that the problem is not an unanticipated problem.
   b. A report is filed in the protocol record, the determination is communicated to the investigator, and no further action is taken.
   c. The reviewer advises the investigator that anticipated problems that are adverse events may be reported in summary form at time of continuing review or status report and that anticipated problems that are not adverse events are non-reportable (see section X.3).
7. If the reviewer considers that the problem was not foreseen (was unexpected/unanticipated) AND determines that participants or others were not harmed, potentially harmed or are at increased risk of harm:
   a. The reviewer indicates that the event, while unanticipated, is not a UPIRSO,
   b. A report is filed in the protocol record and the determination is communicated to the investigator
   c. The investigator is advised to report unanticipated problems affecting the research but NOT involving risks to subjects or others in summary form at time of continuing review or status report (see section X.3).
8. If the reviewer considers that the problem is an unanticipated problem involving, or potentially involving risks to subjects or others, but that the risk is no more than minimal, the reviewer will:
   a. Review the currently approved protocol, consent document and investigators brochure/recruitment documents (if one exists) and;
   b. Review previous reports of unanticipated problems involving risks to participants or others, and
   c. After reviewing all of the materials, the reviewer will take appropriate action depending on the nature of the risk involved, including requiring modification of the protocol or the consent form, if applicable.
   d. The results of the review will be recorded in the protocol record, communicated to the investigator, and reported to the IRB.
   e. All events determined to be unanticipated problems will be reported to the relevant regulatory agencies and institutional officials according to the procedures in Section 11.

8.3.2.2 IRB Review

All reported unanticipated problems where the risk is more than minimal will be reviewed at a convened IRB meeting. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research.

1. The reviewer will conduct their assessment as outlined in section 5 above with the following exceptions:
   a. The reviewer will provide a report summarizing the problem
   b. The convened IRB will review the report and make the final determination regarding how to classify the problem based on the following considerations:
      i. Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
      ii. What action in response to the report is appropriate.
      iii. Whether suspension or termination of approval is warranted.
      iv. Whether further reporting to Institutional and/or federal officials is required.
   c. The convened IRB will specify actions to be taken or will designate a subcommittee or individual(s) with appropriate expertise to ensure that appropriate corrective actions are taken, including but not limited to:
      i. Requiring modifications to the protocol.
      ii. Revising the continuing review timetable.
      iii. Modifying the consent process.
      iv. Modifying the consent document.
      v. Providing additional information to current participants (e.g., whenever the information may relate to the participant's willingness to continue participation).
      vi. Providing additional information to past participants.
      vii. Requiring additional training of the investigator and/or study staff.
      viii. Taking other actions appropriate for the local context.
      ix. Additional actions that may be taken if the event is determined to be a UPIRSO:
         1) Reconsidering approval.
         2) Requiring that current participants re-consent to participation.
         3) Monitoring the research.
         4) Monitoring the consent.
         5) Making referral to other organizational entities (e.g., legal counsel, risk management, Institutional Official).
         6) Suspending the research.
         7) Terminating the research.
   d. The determination of the IRB will be communicated to the investigator along with any corrective actions required

8.3.2.3 Reporting

1. Any suspension or termination of research by the IRB must be promptly reported to the IO, and OHRP (if supported by PHS), and FDA (if FDA-regulated research) through the IO. This should be done in writing.

2. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will
    a. notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, other affected units, and the investigator's supervisor; and
    b. report its findings and recommendations to the IO for further reporting to the appropriate federal officials (eg, NSF, OHRP, and FDA).

8.3 Reporting Other Events

All events, problems, and new information that do not meet the above reporting requirements should be reported to the IRB in summary form at the time of the next continuing review, status report, or protocol closure report.

The IRB recognizes that sponsors may require that the PI report all serious adverse events and safety reports to the IRB. To comply with sponsor requirements, PIs should report adverse events and safety reports that do not meet the above reporting requirements. IRB Administrative Staff will acknowledge receipt of these reports by returning a dated acknowledgement to the PI.