

## Section 14. Reportable Events

The medical school complies with DHHS and FDA regulations that require organizations to have written policies and procedures to ensure prompt reporting of: changes in research activity; unanticipated problems involving risk to subjects or others; and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies.

This section provides definitions and the policies and procedures regarding issues that arise during the conduct of research that must be reported.

### 14.1 Definitions

- **Unanticipated problems involving risk to participants or others:** Unanticipated problems involving risks to subjects or others refers to any incident, experience, outcome, or new information that:
  - Is unexpected.
  - Is related or possibly related to participation in the research.
  - Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal 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 study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.
- **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:** For the purposes of these policies and procedures, an adverse event is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam 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.
- **Unanticipated Adverse Device Effect (UADE):** An Unanticipated Adverse Device Effect means 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 related to the rights, safety, or welfare of subjects [(s)].

- **Protocol Deviations:** A protocol deviation is defined as a variation from the IRB-approved protocol/research plan that happens without prior review and approval of the IRB (eg, study visit outside protocol/research plan window, blood work drawn outside protocol/research plan window, etc.). Depending on the details, protocol/research plan deviations may be determined to be non-compliance (serious, continuing, or otherwise).
- **Protocol Exceptions:** Protocol exceptions are planned deviations from the protocol/research plan. Exceptions are anticipated and must occur with prior agreement from the sponsor, if applicable, and approval by the IRB. If an exception is implemented without IRB approval, it is a deviation, even when the sponsor has approved.

## 14.2 Procedures

### 14.2.1 Reporting

Adverse events in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB as a condition of approval (eg, for first in human clinical trials), the medical school IRB does not accept reports of adverse events and IND Safety Reports that do not meet the definition of an unanticipated problem involving risks to subjects or others.

If investigators are uncertain but believe that the event might qualify as an unanticipated problem, a report should be submitted.

Unanticipated deaths and unanticipated life-threatening serious adverse events must be reported to the IRB immediately after the investigator first learns of the event.

Investigators must report the following events or issues to the IRB as soon as possible, but in no event later than seven (7) working days after the investigator first learns of the event.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (eg, tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an adverse event that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination

that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (eg, a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report.

- An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report.
- A serious adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.
- Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
- Adverse events involving direct harm to subjects enrolled by the investigator (ie, local adverse events), which in the opinion of the investigator or sponsor, may represent an unanticipated problem involving risk to subjects or others.
- An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects (eg, lost laptop).
- An unanticipated event related to the research that results in actual harm or exposes individuals other than the research participants (eg, investigators, research assistants, students, the public, etc.) to potential risk.
- IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
- Data and Safety Monitoring Reports that indicate that risks are greater than previously known or that indicate that the study requires modification or should be suspended or terminated.
- New information that indicates an increase to the risks or decrease to potential benefits of the research. Examples include:
  - 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
  - A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
- New information that may impact the willingness of participants to continue in the research.
- A breach of confidentiality.
- Incarceration of a participant in a study not approved to enroll prisoners.

- Complaint of a subject when the complaint involves the health, safety, or rights of the subject or indicates unexpected risks, possible non-compliance, or cannot be resolved by the investigators and research staff.
- Protocol deviations.
- Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities.
- Unanticipated adverse device effects (UADEs). Regulations require that UADEs be reported to the sponsor and IRB as soon as possible but in no event later than ten (10) working days after the investigator first learns of the event [(a)(1)].
- Any other adverse event or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

### **14.2.2 Submission of Reports**

Investigators and research staff must report possible problems or issues with the research to HRPP/IRB staff in writing using the *Event Reporting Form*. The written report should contain the following:

- Detailed information about the event or issue, including relevant dates.
- Any corrective and preventative actions, planned or already taken, to ensure that the issue or problem is corrected and will not occur again.
- An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any harm (eg, physical, social, financial, legal or psychological) and any plan to address these consequences.
- If a report from a sponsor is the basis for the report of a possible unanticipated problem involving risks to subjects or others, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing:
  - How the event or problem satisfies the definition of an unanticipated problem.
  - Proposed study-wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions.
  - Whether or not the problem has been reported as an unanticipated problem to any relevant federal agencies.
- If a sponsor or lead investigator or coordinating center suspends or terminates some or all research activities, the report should be accompanied by information from the sponsor detailing:
  - Why the suspension or termination was enacted.
  - If it was because of a possible a unanticipated problem (in which case the information in the bullet above must be included).
  - Any impact on subjects or actions to be taken to protect subjects.

- Any plan to inform subjects of the suspension or termination and other pertinent information.
- Whether the suspension or termination has been reported to any relevant federal agencies.
- Any other relevant information.
- Any other information requested by HRPP/IRB staff.

Reports are screened by HRPP/IRB staff and immediately forwarded to the IRB chair or vice chair if HRPP/IRB staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report or complaint from someone other than the investigator or research staff on behalf of the investigator, the IRB chair or vice chair notifies the investigator as appropriate.

### **14.2.3 IRB Procedures for Handling Reportable Events**

Upon receipt of the *Event Reporting Form* from an investigator, HRPP/IRB staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, HRPP/IRB staff contacts 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 HRPP/IRB staff making the correction.

The IRB chair and/or other experienced member(s) designated by the IRB chair receives and reviews the report. The IRB chair (or designee) will make the initial determination as to whether the event is to be regarded as an unanticipated problem and/or non-compliance. (See Section 15 for procedures for unanticipated problems, and Section 16 for serious or continuing non-compliance.)

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 and must follow notification procedures for IRB suspensions.

The IRB or the IRB chair (or designee) has authority to require submission of more detailed contextual information by the investigator, the sponsor, the study coordinating center, or DSMB/DMC about any event occurring in a research study as a condition of the continuation of the IRB's approval of the research.

If the IRB chair or designee determines that the problem does not possibly meet the definition of an unanticipated problem or serious or continuing non-compliance, the reviewer will consider whether any corrective or preventative actions are sufficient and whether modifications to the protocol/research plan, consent, or corrective action plan may be necessary, and refer the matter to the convened IRB for review if appropriate.

The results of the review will be recorded in the study record and communicated to the investigator.

If the reviewer determines that the event is a possible unanticipated problem, the report is reviewed at a convened IRB meeting and must follow notification procedures for addressing unanticipated problems.