# CHAPTER 11

# ADVERSE EVENTS, UNANTICIPATED PROBLEMS, AND PROTOCOL DEVIATIONS IN RESEARCH

## I. ADVERSE EVENTS

### A. Overview

Under federal regulations, investigators conducting research on human subjects are responsible for reporting to the IRB certain adverse and/or unanticipated events that occur during a study, as well as protocol deviations and/or violations. The Adventist HealthCare IRB must review reports of serious adverse events and protocol deviations submitted by investigators to determine if the events involve an increased risk to subjects or have an unfavorable impact on the risk/benefit ratio that was initially agreed to by the subject or considered by the IRB.

### B. Definitions

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| **Adverse event** | Any untoward medical occurrence in a research subject, including any abnormal sign, symptom, or disease, while participating in a clinical trial. There need not be a causal relationship between the occurrence and the subject's participation in the research. |
| **Fatal adverse event** | An adverse event that results in death. (All fatal adverse events are considered serious.) |
| **Serious adverse event** | An adverse event that results in any of the following outcomes:<br>- death,<br>- is life-threatening (places the subject at immediate risk of death from the event as it occurred),<br>- requires inpatient hospitalization or prolongation of existing hospitalization,<br>- results in a persistent or significant disability/incapacity,<br>- results in a congenital anomaly/birth defect,<br>- or any other adverse event that, based on appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. |
| **Moderate adverse event** | An adverse event is an experience that requires medical evaluation (such as additional laboratory testing) and/or therapeutic intervention. If hospitalization is required for treatment, it becomes a serious adverse event. |
| **Anticipated (or expected) adverse event** | An adverse event of a nature, severity or frequency consistent with the current investigator brochure, or with the risk information described in the IRB-approved research protocol or informed consent form. This does not include anticipated events that are more serious than expected or occur more frequently than expected. |

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| **Unexpected adverse event** | An adverse event occurring in one or more subjects of a nature, severity or frequency that is not consistent with either 1) the known or foreseeable risks of adverse events associated with the procedures involved in the research that are in the current investigator brochure, the IRB-approved research protocol or informed consent form, or 2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposed risk factor profile for the adverse event. This includes events that are more serious than expected or occur more frequently than expected. |
| **Unanticipated problem** | An unanticipated problem is any incident or outcome that meets all of the following criteria:<br>- is unexpected (in terms of nature, severity, or frequency) given the research procedures described in protocol-related documents and the characteristics of the subject population,<br>- is related or possibly related to a subject's participation in the research, and<br>- suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) related to the research that was previously known. |
| **Local adverse event** | An adverse event involving a subject enrolled at an Adventist HealthCare facility or other research site that is under the jurisdiction of the Adventist HealthCare IRB. |
| **Non-Local adverse event** | An adverse event observed at an external site (not under the supervision of the Adventist HealthCare IRB). Non-local, or external, adverse events generally are reported to investigators by sponsors of multi-center studies (e.g., external sponsor-generated safety reports). |
| **Definitely related** | The causal link between the adverse event and the research drug, device or intervention is clear. |
| **Probably related** | It is more likely than not that the adverse event may have been caused by the research drug, device or intervention. |
| **Possibly related** | The adverse event may have been caused by the research drug, device or intervention, but there is not enough information to determine the likelihood of causality (or other equally plausible causalities exist). |
| **Not likely related** | There is a low probability that the adverse event may have been caused by the research drug, device or intervention. |
| **Unrelated** | There is no causal link between the adverse event and the research drug, device or intervention. |
| **Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)** | Independent committees established by the sponsor of a study to periodically review and evaluate the accumulated study data for subject safety, study conduct and progress and to make recommendations concerning the continuation, modification, or termination of the trial. Through the sponsor, DSMBs and DMCs provide the PIs with periodic reports summarizing their reviews and determinations. |

### C. Adverse Event Reporting Requirements

The reporting requirements for adverse events vary depending on whether the adverse event occurred locally (i.e., as part of a study overseen by the Adventist HealthCare IRB) or non-locally (i.e., at another site in a multi-site study). For non-local adverse events, the reporting requirements depend on whether the non-local study has an independent DSMB or DMC that reviews adverse events. The matrix below captures Adventist HealthCare's adverse event reporting requirements.

| Location of adverse events | Investigators must report adverse events which are: |
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| **Local adverse event** | (1) expected or unexpected,<br>(2) of moderate or serious severity, **and**<br>(3) possibly, probably or definitely related to the subject's participation in the research. |
| **Non-Local adverse events in studies without a DSMB or DMC** | (1) unexpected,<br>(2) of moderate or serious severity, **and**<br>(3) possibly, probably or definitely related to the subject's participation in the research. |
| **Non-Local adverse events in studies with a DSMB or DMC** | (1) unexpected,<br>(2) possibly, probably or definitely related to the subject's participation in the research, **and**<br>(3) suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) related to the research than was previously known.*.<br>*If uncertain whether an event places subjects or others at a greater risk of harm than was previously known, consider if the event requires revision to the protocol or informed consent as will usually be the case if the event meets this reporting criteria. There are, of course, situations that would not warrant revisions, but these would be rare. |

Note: Research sponsors may have adverse event reporting requirements that differ from Adventist HealthCare's policies. Investigators are requested to contact the IRB Administrator to discuss how Sponsor requirements may be satisfied.

### D. Format of Adverse Event Reports

Only adverse events that meet the criteria listed above must be reported to the IRB. Local adverse events that meet the criteria above must be reported to the IRB using both the Adverse Event Reporting Form and the Adverse Event Cumulative Table. If additional relevant documents exist (e.g., a copy of the completed FDA MedWatch report form or an autopsy report), these should be submitted to the IRB as well.

Adventist HealthCare recognizes that some sponsors require PIs to submit adverse event information that is outside the scope of this Adventist HealthCare policy. The IRB Administrative Office will acknowledge receipt of all non-local adverse events that do not meet

the criteria listed above. These non-local adverse events outside the scope of this policy are to be reported using only the Adverse Event Cumulative Table. Upon receipt of the Adverse Event Cumulative Table, the IRB Administrative Office will provide acknowledgement of receipt and maintain submitted reports and forms in the official IRB file. These documents will be made available to regulatory authorities upon request. The IRB will review the Adverse Event Cumulative Table that includes all local and non-local adverse events at the time of continuing review.

The Adverse Event Reporting Form and the Adverse Event Cumulative Table require the PI to assess the causality of the event, the seriousness of the event, and whether or not the event was expected. In addition, the Adverse Event Reporting Form solicits the PI's advice regarding what, if any, action should be taken in light of the adverse event.

The Adverse Event Cumulative Table tracks the local and nonlocal adverse events submitted for a particular study. The Table must be updated to reflect (1) each local adverse event reported to the IRB and (2) each non-local adverse event report received by the investigator from the sponsor of a multi-site study.

### E. Timing of Adverse Event Reports

The Adverse Event Reporting Form and Cumulative Table must be submitted within ten (10) working days of the adverse event (for local events) or within ten (10) working days after the investigator receives notice of the adverse event from the sponsor (for non-local events meeting the reporting requirements). Additionally, for local events that are related and fatal or life-threatening (i.e., the subject was at immediate risk of death from the event), an IRB Administrative staff member and/or IRB Chair must be **initially** notified via **email** of the occurrence within 48 hours. The standard IRB Adverse Event Reporting Form and Cumulative Table must then be submitted pursuant to standard reporting requirements (i.e., within ten (10) working days).

### F. Timing of DSMB or DMC Reports

Reports from DSMBs and DMCs must be submitted to the IRB within ten (10) working days of the PI's receipt.

### G. Reports to FDA

In addition to the reporting requirements outlined in section C above, and as addressed more fully in Chapter 8, investigators and/or other parties are responsible for reporting certain adverse events to the FDA and to the Sponsor of the study. Refer to Chapter 8 for additional information pertaining to these requirements.

### H. IRB Review of Adverse Events

When reviewing adverse event reports, the IRB will consider whether the event impacts the risk/benefit ratio of the study to ensure adequate protection of the welfare of subjects. Based on this review, the IRB may (1) acknowledge the adverse event but take no additional action, (2) request additional information about the adverse event, (3) require modifications to the protocol and/or the informed consent form, (4) revise the continuing review timetable, or (5) reconsider approval of the study.

## II. UNANTICIPATED PROBLEMS

Principal Investigators are required to report all unanticipated problems to the IRB. In addition, federal regulations require that the IRB promptly report any unanticipated problems involving risks to subjects or others to the Office of Human Research Protections (OHRP) and/or the Food and Drug Administration (FDA). if the research is conducted under a Federal Wide Assurance.

### A. Definition and IRB Review

An unanticipated problem is any incident or outcome that meets all of the following criteria:

1. is unexpected (in terms of nature, severity, or frequency) given the research procedures described in protocol-related documents and the characteristics of the subject population,

2. is related or possibly related to a subject's participation in the research, **and**

3. suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) related to the research that was previously known.

**Some adverse event may meet the criteria of an unanticipated problem listed above.**

An unanticipated problem is a reportable event even if no harm occurs. Social harm may result in well-defined events such as loss of employability, loss of insurability, and criminal or civil litigation, but more commonly it disrupts interpersonal relationships by causing embarrassment, humiliation, discrimination, or stigmatization. Examples of social and psychological harm are:

- loss of records or computer participant information;
- breach of confidentiality;
- loss of employability;
- loss of insurability; and
- criminal or civil litigation

When reviewing unanticipated problems, the IRB will determine if any of the following corrective actions or substantive changes might need to be considered in response to an unanticipated problem:

- 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; and/or
- provision of additional information about newly recognized risks to previously enrolled subjects.

All unanticipated problems will be reviewed by full committee review. When reviewing a report of an unanticipated problem, the IRB will consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be expected to result. The IRB may determine that the problem does not meet the criteria for an unanticipated problem. If so, further reporting to institutional officials, the department head (or designee), and OHRP will not be required.

### B. Format of Unanticipated Problem Reports to the IRB and Reporting Timeline

In order for the IRB to fulfill the requirement to report all unanticipated problems to OHRP, the Principal Investigator must complete an incident report containing the following information:

1. institution conducting the research (e.g., university, hospital, foundation, etc.);

2. title of the research project and/or grant proposal in which the problem occurred;

3. name of the Principal Investigator on the protocol;

4. number of the research project assigned by the IRB and the number of any applicable federal award;

5. a detailed description of the problem; and

6. actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)

## III. Protocol Deviations and Violations (21 CFR 55.108(a)(4); 45 CFR 46.103(b)(4)(iii); ICH GCP Art. 4.5.2, 4.5.4)

### A. Overview

A protocol deviation is an unanticipated or unintentional divergence or departure from the expected conduct of an approved study that is not consistent with the current research protocol, consent document or other approved study documents. Examples of protocol deviations include:

- enrollment of subjects outside protocol inclusion/exclusion criteria, whether agreed to by the sponsor or not;
- medication/intervention errors (e.g., incorrect drug/intervention, incorrect dosage of the drug);
- research procedures or visits conducted outside the prescribed window of time;
- changes in procedures initiated to eliminate immediate hazards to study subjects;
- inadvertent deviation in specific research intervention procedures or timing of the research intervention which could impact the safety or efficacy of the study-related intervention or upon the experimental design (usually this would not include appointment deviations);
- breach of confidentiality or privacy whereby confidential information about a subject is revealed in inappropriate settings, to persons without a need to know, or by data exposure (e.g., computer security breach, documents left unsecured); and
- deviation from the consenting process described in the protocol (e.g., unapproved individual conducting informed consent discussion; English consent form used to consent a non-English speaking patient; an unapproved translated consent document used to consent a non-English speaking subject).

### B. Protocol Deviation Reporting Requirements

The following types of protocol deviations must be reported in writing to the IRB **within seven (7) working days** of their occurrence or of the Principal Investigator becoming aware of the deviation using the "Protocol Deviation Reporting Form":

- deviations that may affect the risk/benefit analysis of the study;
- deviations that may affect the rights, health and/or welfare of a subject;
- deviations that may affect the safety and/or privacy of a subject; and
- deviations that may affect a subject's willingness to participate.

**All other deviations must be tracked by PI or his/her team and reported on the Protocol Deviation Cumulative Table as part of the Continuing Review process.** The table below should be used as a guide when determining whether a Protocol Deviation is significant enough to require completion and submission of the Protocol Deviation Reporting Form.

| Examples of protocol deviations requiring the PI to submit a Protocol Deviation Reporting Form to the IRB within seven days | Examples of protocol deviations that do not require submission of a Protocol Deviation Reporting Form (and need only be reported as part of Continuing Review) |
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| • Use of invalid consent form (e.g., consent form without IRB approval stamp, outdated/expired consent form)<br>• Over-enrollment (enrollment above the number approved by the IRB)<br>• Improper release of confidential subject information<br>• Enrollment of subjects after IRB-approval of study expired<br>• Enrollment of a subject who did not meet all inclusion/exclusion criteria<br>• Performing study procedure not approved by the IRB<br>• Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity<br>• Study medication dispensing or dosing error<br>• Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety<br>• Failure to follow safety monitoring plan<br>• Study drug improperly unblinded by study personnel<br>• Research procedures performed by individuals not approved for participation by the IRB | • Missing original signed and dated consent form (but a photocopy is available)<br>• Missing pages of executed consent form<br>• Copy not given to the person signing the form<br>• Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity<br>• Omitting an approved portion of the protocol<br>• Failure to perform a required lab test<br>• Missing lab results<br>• Study procedure conducted out of sequence<br>• Study visit conducted outside of required timeframe |

## IV. Policy Compliance IRB Responsibility for Reporting

As mentioned in Section II above, the IRB must report any unanticipated problems involving risks to subjects promptly to OHRP and/or the FDA. Depending on the circumstances of the problem, it may be appropriate for the IRB to send an initial report, and indicate that a follow-up report will be submitted by a specific date or when an investigation has been completed or a corrective action plan has been implemented, whichever occurs first.

All unanticipated problems will be reported to and reviewed by the IRB. In addition, all local unanticipated problems will also be reported to the Senior Vice President and Chief Quality & Integrity Officer, and the Vice President of Quality (or Compliance) of the entity at which the

protocol is approved within one month of receipt of the report. The Medical Executive Committee will receive monthly IRB minutes, once approved by the IRB, which will address all unanticipated problems.

The IRB Administrator is responsible for the reporting of all local unanticipated problems to OHRP and the supporting HHS agency head (or designee) within one month of receipt of the report of the problem from the Principal Investigator.

In addition to reporting unanticipated problems involving risks to subjects or others, the IRB is also responsible for reporting any serious or continuing noncompliance and any suspension or termination of IRB approval. The IRB Administrative staff will report any serious or continuing noncompliance to the IRB and the Vice President of Quality (or Compliance) of the entity at which the protocol is approved.

Investigators are requested to review Chapter 7 of the IRB Handbook for guidance on investigator responsibilities. It is imperative that investigators familiarize themselves with the reporting responsibilities addressed in this policy.

*Serious noncompliance* is defined as noncompliance that resulted in increased risks to research participants or to any individual involved or affected by the research project.

*Continuing noncompliance* is defined as a pattern of noncompliance that suggests an underlying deficiency in human subject research knowledge.