Reporting Requirements for Studies Involving Other Investigational Agents, including Investigational Drugs

Introduction

“Adverse events” (AEs) (additionally referred to as “adverse experiences” in the FDA regulations) are events that happen to subjects during or after participation in drug, biologic or device trials and relate to the possible safety of the drug, biologic or device. Because of past over-reporting of AEs on FDA-regulated trials to the IRB, the UW-Madison HS IRBs Office has developed guidelines regarding which AEs need to be reported to the IRB. With the exceptions noted below, only AEs that meet the definition of unanticipated problems are required to be reported to the IRB.

This set of guidelines addresses only the reporting to the University of Wisconsin-Madison HS IRBs of AEs that occur on FDA-regulated trials involving drugs or biologics. Special guidelines cover the reporting of AEs for VA studies and gene transfer studies.

NOTE: These guidelines do not substitute for the researcher’s duty to report AEs to the sponsor of the research or to other bodies, such as the FDA, Madison VA, University of Wisconsin Hospital and Clinics, or the Clinical and Translational Research CoreUnit.

Please note that the reporting requirements for AEs that occur on research studies involving investigational devices are unique and are described in the Reporting Requirements for Studies Involving Investigational Devices.

The AE reporting guidelines must be used in tandem with the UW-Madison Unanticipated Problems Policy because some events, problems, or information should also be reported to the IRB as “unanticipated problems,” as defined in the Unanticipated Problems Policy. The Unanticipated Problems Policy describes events that may not be directly related to the drugs and biologics under study, but may still require reporting to the IRB.

The objective of this document is to provide the University of Wisconsin-Madison research community with guidelines regarding:

1. Which AEs require reporting to the IRB
2. The timeframe for reporting AEs to the IRB
3. The format and information required in a report of an AE
Adverse Events Requiring Reporting to the IRBs

Whether an AE requires reporting to the IRB depends on whether it was (a) unexpected or unanticipated; (b) involves risks to the subject or others; and (c) reasonably related to the study treatment or intervention. Of primary concern to IRBs are AEs that are serious, unexpected, and probably related to the study treatment or intervention. In contrast, AEs that are expected, do not involve risks to subjects (or others), or which are unrelated or unlikely to be related to study participation do not require prompt reporting after the AE occurs and may not need to be reported to the IRB at all.

For example, events that are expected even though they may involve risks to subjects or others would be disclosed to the IRB at the time of the initial review of the protocol, as well as mentioned in the consent form and/or Investigator’s Drug Brochure or Package Insert. The IRBs take into consideration these expected risks as part of their determination as to whether the protocol can be approved for enrollment of human subjects (i.e., the risks to subjects are minimized and reasonable in relation to anticipated benefits). These events would not require further reporting unless the frequency with which the event occurs is higher or the event more severe than originally anticipated. The specific details regarding which AEs require reporting and when they are to be reported to the IRB are outlined below.

Similar to other IRBs, the Health Sciences IRBs assume greater oversight over local AEs. For multicenter trials, the Health Sciences IRBs will rely primarily on the Data Safety Monitoring Boards (DSMBs) or Data Monitoring Committees (DMCs), when they exist, to evaluate AEs. DSMBs and DMCs are expected to be in the best position to evaluate whether these events present risks to subjects on a research study. Consequently, reporting requirements for AEs that occur on multicenter trials will differ depending on whether a DSMB or DMC exists.

Definition of Serious Adverse Event (SAE)

As noted previously, AEs that are deemed serious are of primary concern to IRBs. In order to assist researchers in determining whether an event qualifies as serious, the Health Sciences IRBs have adopted the following definition of serious, which is similar to the FDA definition. Serious AEs are those that are any of the following:

- fatal
- life-threatening
- persistent or significantly disabling or incapacitating
- an inpatient hospitalization or prolongation of hospitalization
- a congenital anomaly or defect
- a significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above

The VA further defines serious adverse events as those that require medical, surgical, behavioral, social, or other intervention to prevent a serious outcome as described above.
The definition of an SAE is relevant to the identification of which events require reporting to the IRB and Associate Chief of Staff for Research under current VA guidance. See the section below of reporting adverse events for studies involving the Madison VA.

**Adverse Events that are Reportable to the IRBs**

Federal regulations, including those of the Department of Health and Human Services (DHHS) and the FDA, require institutions engaged in human subjects research to have written procedures for ensuring prompt reporting to the IRB of “unanticipated problems involving risks to subjects or others.” [45 CFR 46.103; 21 CFR 56.108]. “Unanticipated problems involving risks to subjects or others” is a broad term, which includes not only unfavorable outcomes that have occurred that were not expected, but also the development of potentially increased risks of harm occurring in the future.

In January 2009, the FDA adopted guidance regarding which adverse events, described below, should be reported to the IRB and identified those that are likely to represent unanticipated problems involving risks to subjects or others.

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, Stevens-Johnson Syndrome);
2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control).
4. An AE that is described or addressed in the investigator’s brochure, protocol, or informed consent documents that occurs at a specificity or severity that is inconsistent with prior observations OR for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence.
5. Any AE or safety finding (e.g., based on animal or epidemiologic data) that 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.

**When to Report an Adverse Event to the IRBs**

The timing and format for submitting an AE report to the IRBs depends on whether: (a) the event suggests an adverse alteration in the risks to subjects or others; (b) the event is reasonably related to study participation; (c) the event is unexpected; (d) there is a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC); (e) the
event occurred at sites or to subjects under UW purview; (f) the event results in or is expected to result in a change to the protocol, consent documents, and/or dissemination of new information to subjects (e.g., letter or telephone call to subjects); and (g) whether an investigational device is involved.

A. **Immediate Report to the IRB**
An AE, regardless of where it occurred, which meets all three of the following conditions must be reported to the IRB immediately:

1. Unexpected
2. Immediately life threatening or severely debilitating to other current subjects, and
3. Caused by or probably related to the treatment or study intervention.

The IRBs expect that these reports will be rare. AEs that meet these conditions must be reported to the IRB Chair or IRB Director via telephone as soon as possible, but no later than 1 business day after the local research team becomes aware of the event. The research team will then discuss with the IRB Chair or IRB Director what action needs to be taken related to the occurrence (e.g., suspension of study enrollment, change in treatment regimen) to prevent further harm from occurring. This initial report to the IRB Chair or IRB Director must be followed within 2 business days with a submission of an Adverse Event Report Form to the IRB Office.

B. **Report to the IRB within Five (5) Business Days: VA Studies Only**
See [Reporting Guidelines for VA Protocols](#) for details.

C. **Report to the IRB within Fourteen (14) Business Days**
Any other AE as described above Adverse Events that are Reportable to the IRBs must be reported to the IRB within fourteen (14) business days.

D. **Report to the IRB at Continuing Review**
AEs that meet the criteria below should be reported at the time of continuing review. Events reported at continuing review must meet ALL of the following criteria:

- Occurred locally (i.e., at sites under UW IRB purview);
- Are related to the research study but unexpected;
- Were not assessed as placing subjects or others at increased risks (including physical, psychological, economic, or social harm) than was previously known or recognized;
- Were not assessed as resulting in new information that needed to be disseminated to participants; and
- Occurred on studies that do not have a formal DSMB or DMC

**Adverse Events That Should Not Be Reported to the IRB**
If AEs do not meet the criteria outlined above, they do not need to be reported to the IRB unless the study falls under Madison VA purview or involves gene transfer. The
following AEs should not be reported to the IRB for non-VA or studies that do not involve gene transfer:

- AEs that are not related to the study intervention or treatment.
- AEs that are expected.
- AEs that do not involve risks to subjects or others.
- Events that occur on studies that have a formal, independent DSMB or DMC and do not otherwise result in a change to the research study, including revisions to consent documents or the protocol, or suggest new information that should be disseminated to subject.

Reporting Guideline for VA Protocols
All AEs that occur in subjects under UW-Madison IRB purview who are enrolled in research studies that have been reviewed and approved by the Madison VA’s Research & Development Committee (i.e., fall under Madison VA purview) that are considered to be serious as defined above and determined by the Principal Investigator to be unanticipated must be reported by the research team to the IRB and Associate Chief of Staff for within 5 business days of the local research team becoming aware of the event. This includes AEs that related or unrelated to the research.

Reporting Guidelines for Protocols Involving Gene Transfer
Reporting AEs for protocols involving gene transfer generally parallel those described above. However, because of the nature of these research studies, additional oversight is required. The following exceptions to the guidelines apply to gene transfer protocols:

- All AEs for any protocol involving gene transfer that are serious and unexpected, regardless of their suspected relationship (or lack thereof) to the study intervention or whether a formal DSMB or DMC exists for that study, must be reported to the IRB within 14 business days of the investigator becoming aware of the events.
- All deaths of subjects participating in gene transfer protocols must be reported to the IRB regardless of the length of time after the last treatment was administered. Deaths must be reported within 14 business days of the investigator becoming aware of the events.

Format of Adverse Event Reports
The format of an AE report to the IRB depends on the required timing of the report and whether the report results in a change to the protocol, revisions to consent documents, and/or dissemination of new information to subjects. Refer to the Unanticipated Problems/Adverse Event Reporting Decision Guide.

- Immediate (with 2 business days after initial reporting to the IRB Chair or IRB Office Director)
  o Forms required: Serious Adverse Event Report Form, Change of Protocol Form (if applicable)
- Within 5 or 14 business days
- Forms required: Serious Adverse Event Report Form, Change of Protocol Form (if applicable) – ensure report is sent to the VA

- **At continuing review**, no change anticipated
  - Forms required: Continuing Review Protocol Progress Report Form, a copy of the most recent DSMB/DMC report (if applicable), and a spreadsheet that describes all local AEs that have occurred (regardless as to whether they have been reported to the IRB previously), their possible relation to study intervention, and whether the event(s) resulted in a protocol or consent form change

### Relevant Regulations and Guidance Governing AE Reporting

- 45 CFR 46.103 (HHS) assuring compliance
- 21 CFR 56.108 (FDA) IRB functions and operations
- 21 CFR 312.32 (FDA) reporting requirement for sponsors
- 21 CFR 312.53 (FDA) reporting rules in drug trials
- 21 CFR 312.64 (FDA) reporting obligation for investigators in drug trials
- 21 CFR 312.66 (FDA) reporting requirements for drug trials
- 21 CFR 812:150 (a) (FDA) reporting requirements for device trials - investigator
- 21 CFR 812.150 (b) (FDA) reporting rules for sponsors in device trials – sponsor
- Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, Dept. of Health and Human Services, Office for Human Research Protections (OHRP), January 15, 2007
- VHA Handbook 1058.01, Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight, Department of Veterans Affairs, May 21, 2010

### See Also:

- [Reportable Event Submission Instructions](#)