Ascension Wisconsin IRB Guidance

Reportable Events: Non-Compliance, Safety Information and Unanticipated Problems

Federal regulations 45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others. The IRB will review the reports and fulfill reporting requirements to the appropriate institutional officials and federal departments or agencies.

Ascension Wisconsin requires Investigators to promptly report all events that may constitute unanticipated problems involving risk to research subjects or others (referred to hereafter as "unanticipated problems") and new or updated safety information. The following Reportable Events must be reported to the IRB within 5 business days after the Investigator becomes aware of the event.

What needs to be Reported Promptly to the IRB

The IRB SOP: Reportable Events (New Information) outlines the IRBs reporting requirements. This guidance provides supplemental information to help researchers determine whether or not an event meets the IRB requirement for prompt reporting.

In general, any event that has an impact on the rights, welfare or safety of subjects, or that impacts the integrity of the study should be evaluated to consider if it meets these requirements. Examples are provided later in this document.

Useful definitions include:

- Adverse Event (AE): Any unfavorable or unintended event, including abnormal laboratory findings, symptom or disease, or death associated with the research or the use of a medical investigational test article. An AE in research may occur even in the absence of any error or protocol deviation and does not necessarily have to be caused by any identifiable aspect of the research.
- Serious Adverse Event (SAE): Is an AE that results in death, is life-threatening, results in or prolongs inpatient hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, results in overdose/error of drug or biological product, or is an important medical event that jeopardizes the subject or requires medical intervention to prevent one of the outcomes listed above.
- Problem Related to the Research: The event arises from the conduct of the research and is of concern for subjects or others directly affected by the research. Problems may be attributable to the conduct of the research, or may result from failures or errors in general systems outside the research, or factors that are not controlled by the researcher under the protocol, but on which ethical conduct of the research depends, according to the protocol.
- Unanticipated Problem Involving Risks to Subjects or Others ("Unanticipated Problem" or UPIRSO"): Any event that is 1) unexpected in nature, severity, or frequency; 2) related or possibly related to participation in the research; and 3) places subjects or others at a greater risk of harm than was previously known or recognized.
- Related: More likely than not, caused by the study product or study procedures ("possibly related" or "definitely related").
- Unanticipated: The event is unexpected in nature, frequency, or severity; or, if anticipated, is not fully addressed or specified in the initial protocol application, any amendments, consent documents, investigator brochures, IRB minutes, and any existing documentation regarding the research conducted to date under the protocol.

How to Determine if an Adverse Event is Considered an Unanticipated Problem

The majority of adverse events occurring in human subjects are not unanticipated problems. Only Unanticipated Events must be reported promptly to the IRB.

To determine if an adverse event is an unanticipated problem, ask the following:

a. Is the adverse event unexpected?
b. Is the adverse event related or possibly related to the study product or study procedures?
c. Is the adverse event serious, or suggest the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is yes, then the adverse event is an unanticipated problem and must be reported to the IRB within 5 business days after the PI becoming aware of the event. If an adverse event does not meet all three requirements, it is not an unanticipated problem, and therefore does not need to be promptly reported to the IRB.

Problems that Must be Reported and How to Submit to the IRB

Event	**Examples** (not all-inclusive)	**Reporting Criteria**	**How to Report** (forms in Mentor)
Adverse Events at the local site (AEs that are an unanticipated problem)	- Cardiovascular event induced by study device. - Significant allergic reaction from study drug. - Multiple occurrences of an AE that, based on aggregate analysis, meets reporting criteria. - An AE that is described or addressed in the investigator's brochure, protocol or informed consent documents but that occurs at a severity or frequency that is inconsistent with prior observations or expectations.	An adverse event that is: - Serious, **and** - Unanticipated, **and** - Related to the study *Adverse events that do not meet the criteria listed above DO NOT need to be reported to the IRB.*	Local Unanticipated Problem Report Form
External Serious Adverse Events	- IND Safety Reports - MedWatch Reports - CIOMS Reports - Any other AE 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.	Unanticipated problem that adversely affects the: - risk/benefit ratio of the study, **or** - rights, safety, or welfare of subjects, **or** - integrity of the study.	Safety or New Information Update Form Include a copy of External SAE report and Sponsor summary and/or assessment.
Other Unanticipated Problem	- Participant unexpectedly becomes pregnant. - Breach of subject confidentiality (e.g. loss of a laptop with PHI or sensitive information). - A pharmacy error resulted in a higher dose of investigational drug than dictated by the IRB-approved protocol (whether or not the subject had adverse events).	An event that is: - Unanticipated, **and** - Related to the study or is of concern for subjects, **and** - Placed subjects or others at greater risk of harm.	Local Unanticipated Problem Report Form
Serious Non-Compliance or Continuing Non-Compliance	- Failure to obtain informed consent. - Performing study procedures before IRB approval is obtained. - Continuation of research after IRB approval has lapsed. - Performing activities not described in IRB-approved protocol. - A self-assessment of 40 study consent forms indicates that 25 were missing signature dates.	An intentional or unintentional change from IRB-approved protocol that adversely affects the: - risk/benefit ratio of the study, **or** - rights, safety, or welfare of subjects, **or** - integrity of the study.	Significant Protocol Deviation/Noncompliance Report Form
Research Complaint	- Subject complaint regarding a research-related injury or study activities. - Complaint from study personnel regarding fabrication of data or research misconduct.	A complaint associated with the study regarding an alleged breach of the: - rights, safety, or welfare of subjects, **or** - integrity of the study.	Local Unanticipated Problem Report Form

Adverse Audit or Enforcement Actions	- FDA form 483 - Adverse Sponsor audit results - Suspension or restriction of medical license	An adverse finding issued to, or enforcement action taken against the PI.	Local Unanticipated Problem Report Form Include a copy of the audit results, enforcement action, etc.
Reports, publications, or interim results or findings	- DSMB reports (with findings or recommendations other than continuation as planned) - FDA Public Health Advisory - "Dear Healthcare Professional" letter	All reports, publications, or interim results or findings.	Safety or New Information Update Form Include a copy of report, publication, interim finding, etc.
New or updated study product safety information	- Revised Investigator's Brochure - Revised label/package insert - Device manual	All new or updated study product safety information and a summary of changes.	Safety or New Information Update Form Include a copy of new or updated product safety information.
Recalls, Withdrawals, or Clinical Holds	- Early study termination - FDA or Sponsor withdrawal	Correspondence communicating a FDA or Sponsor mandated marketing recall, withdrawal or clinical hold.	Safety or New Information Update Form Include a copy of the correspondence.

Events that Do Not Meet the IRB's Requirements for Prompt Reporting

Events that do not meet the IRB's reporting requirements do not need to be reported to the IRB. Examples of such events are:

a. Minor protocol deviations (e.g., study visit performed slightly out of window)
b. Adverse events that, in the PI's judgment, are not related to the study
c. Adverse events that are anticipated or expected as part of the study
d. External Serious Adverse Event reports (for example IND safety reports) that, in the PI's judgment, do not affect the conduct of the study at WFH do you want Ascension?

The IRB recognizes that Sponsors may have policies that require reporting of all events to the IRB (regardless of whether the IRB would require reporting or not). The IRB asks that study teams first provide the Sponsor with the SOP: Reportable Events (New Information) and explain that the item does not meet local reporting requirements. If the Sponsor still requires submission, the item can be submitted in Mentor as an administrative review and the IRB will provide a standard acknowledgement of items submitted to fulfill Sponsor requirements.

The Principal Investigator is responsible for meeting obligations to report events to the Sponsor, the FDA and the data safety monitor- which may be different from the IRB reporting requirements. Additionally, study teams typically maintain records of all adverse events and protocol deviations that occur at the site. At the time of continuing review, the IRB Continuing Report Form may request that the PI submit the summary of adverse events or log, minor noncompliance and protocol deviations for further consideration by the IRB.

REFERENCES

- 21 CFR §56.108(b)
- 45 CFR §46.103(b)(5), 45 CFR §46.108(a)
- IRB-SOP Reportable Events (New Information) (SOP-204)
- OHRP Guidance on Reviewing and Reporting Unanticipated Problems and Adverse Events: http://www.hhs.gov/ohrp/policy/AdvEvntGuid.html
- FDA Guidance: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf