

# I2F PR1 Reporting Adverse Events to the IRB

---

## Overview

This procedure describes the process whereby certain types of adverse events are reported to the Institutional Review Board (IRB) by a University of Nevada, Reno (the University) or affiliate principal investigator.

## I2F1 Format of Adverse Event Reports

Reports to the IRB must be in writing using the *Report of Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others* (AE Report) for reporting serious, unanticipated\* adverse events (AEs) under a University or affiliate Principal Investigator (PI). For reporting AEs from external sites under a multi-center research protocol, the investigator must provide aggregated data and an analysis or summary from the sponsor or Data Safety Monitoring Board (DSMB), when applicable and available, sufficient to explain the significance of the event or series of events along with the AE Report.

\*“Unanticipated” includes expected adverse events that occur in greater frequency or severity than originally anticipated.

External AEs that don't qualify as serious, unanticipated or possibly related must be tracked on a non-reportable events log and submitted at the time of continuing review. It is sufficient for the log indicate that adverse events have occurred at the expected frequency and level of severity as previously documented.

Comprehensive data collection about all adverse events that occur in human research is mandatory. Such data need to be (and are) routinely collected by study personnel, and routinely reported to the sponsor. The sponsor then may have obligations to report such data to regulatory agencies (such as the FDA in cases where drugs are involved). The sponsor also has obligations to keep investigators updated in terms of any new information and therefore will forward reports of adverse events to all principal investigators. These reports often come with a request or demand to forward such reports to the local IRB and consequently, are often submitted to the IRB as requested by the sponsor whether or not a given report meets the local IRB's standards for reporting adverse events. The University IRB neither requires nor accepts AE reports unless the event meets the criteria for a local unanticipated adverse event, external unanticipated serious adverse event or unanticipated problem involving risks to subjects or others (as defined in Policies I5D Noncompliance or I2F Reporting Adverse Events and Unanticipated Problems. All reports failing to meet the criteria will be returned to the investigator.

## II2F2 Examples of Adverse Events Reportable as Serious Adverse Events

1. Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
2. A series of adverse events that, on analysis, is both unanticipated and a problem for the study. There would be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and significantly affected the rights and welfare of participants. A summary and analysis supporting the conclusion must accompany the report.
3. An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, or expected to occur in study participants at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in participant population), but that occurs at a greater frequency or at greater severity than expected. A discussion of the divergence from expected rates must accompany the report.
4. Any other adverse event 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 assure the protection of human participants. An explanation of the conclusion must accompany the report.

## II2F3 Investigator Evaluation of Adverse Events

The investigator must evaluate all adverse events and assess any potential effects of the event on the risks or benefits of participation. Following these assessments, the PI must then determine if modifications to the protocol, the consent form or both are warranted.

Depending on the outcome of her or his assessment, the Investigator may consider suspending the protocol pending

1. further review,
2. notification of current or past participants, or
3. changes to participant monitoring plans.

If a local adverse event is determined to be serious and unanticipated (whether or not drug related), or an external event increases risks, decreases benefits, or requires modifications to the protocol, the investigator must promptly submit an AE Report and an amendment request (if changes are warranted) to the IRB (within five days unless the event was fatal or life-threatening, in which case it should be reported within 48 hours).

## Reports of External Adverse Events Reports for Multi-Center Studies

For multicenter studies the University or affiliate investigator must submit a report which provides aggregated data and an analysis or summary explaining the significance of the adverse event or series of events in order to ensure the information is interpretable and relevant to the IRB's task of protecting the rights and welfare of human participants. The IRB recognizes that the sponsor, because it receives adverse event information from all study sites, is in a better position to process and analyze the significance of adverse event information. Therefore, an investigator may rely on the sponsor's assessment and provide to the IRB a report prepared by the sponsor or DSMB, if applicable and when available. The report should evaluate the event and make a determination as to whether the adverse event affects the risk-to-benefit ratio of participating in the study and whether modifications to the protocol, consent form or both are required. If so, the adverse event form and an amendment request should be submitted promptly to the IRB (within five business days upon receipt of the sponsor or monitoring entity report).

## I12F4 Considerations for Investigator Evaluations of Adverse Events

Reviewing reports of certain types of adverse events that may affect participants' welfare, requires investigators to think about and implement participant protections. Consideration should involve assessing whether there has been a change to the risk-to-benefit ratio, assessing whether changes are required to the protocol or procedures in order to minimize risks, and deciding whether changes are required in the information shared with current, potential, and previously enrolled subjects (as reflected in the consent form).

## Categorical Assessments of Adverse Events

### Seriousness

The nature of the event such as "serious" versus "non-serious." Serious events can encompass physical, psychological, social, legal, and economic harm, harm to dignity, and unexpected threats to privacy or safety.

When applied to a protocol involving drugs, FDA defines "serious" as any adverse experience resulting in death, a life-threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

### Expectedness

The following questions may be used to assess the "expectedness" of an event:

1. Was the event was anticipated or unanticipated at the time of study design?
2. Does the event suggest that the research places participants at greater risk of harm than was previously known or recognized?

3. Did the frequency of anticipated, related events exceed expectations?

Anticipated events must be listed as potential risks in the protocol and the consent form, and the likelihood of occurrence indicated in an understandable way (e.g. x number of people out of 100).

### Relatedness

The “relationship” of the event to the study is based on the degree to which the procedure or intervention used in research may have reasonably caused the event. The concept of relatedness is often thought of in terms of degree, such as

1. unrelated,
2. unlikely to be related,
3. possibly related or
4. probably or definitely related.

The expectedness or relatedness of a single AE occurrence when viewed as isolated events cannot be fully assessed nor can implications for the research study be determined. Many types of AEs require an evaluation of their relevance and significance to the study, including an aggregate analysis of other occurrences of the same (or similar) event, before they can be determined to be an unanticipated problem involving risk to human subjects. In multi-center trials, individual investigators rely on the sponsor to provide them information about AEs occurring at other study sites. Sponsors are required to consider a report of an AE within the context of other AE reports. Additionally, because the sponsor is in the best position to determine if an AE is an unanticipated problem the investigator in a multi-center trial may rely on the sponsor’s assessment and provide to the IRB a report of an unanticipated problem prepared by the sponsor.

Local serious adverse events that are uncommon and strongly associated with drug exposure would be considered unanticipated problems and should be reported by the investigator to the IRB.

## II2F5 Reporting Adverse Events Involving Investigational Devices

Investigational device exemption regulations require investigators to report to the sponsor any serious adverse effects on the health or safety of research subjects or any life-threatening problem, or death caused by or associated with a device if the effect was not anticipated at the time the research was planned, or the effect was more severe or effects were more frequent than originally anticipated.

Sponsors must assess each report of an unanticipated adverse device effect and report the evaluation results to the FDA, and all reviewing IRBs and participating investigators within 10 days of receipt of the report.