Policy II2F Adverse Events and Unanticipated Problems

Scope

This policy defines the reporting requirements for adverse events and unanticipated problems involving risks to subjects (or participants) or others (henceforth referenced as Unanticipated Problems). This policy applies to all research approved by the University of Nevada, Reno (the University) Institutional Review Board (IRB) or research determined the University Human Research Protection Program (HRPP) (comprised of the Office of Human Research Protection [OHRP] and the IRB) to qualify for exemption.

Incidental findings which were anticipated, unless determined to be serious adverse events (see definition below), do not qualify as Unanticipated Problems and are instead covered in Policy II2I Findings with Possible Health and Safety Significance for Research Participants.

Policy Statement

Investigators conducting research involving human participants must notify the IRB within five business days of discovery any unanticipated adverse event that occurred locally, and any serious adverse event or any Unanticipated Problem that occurred in the course of research approved or deemed exempt by a University IRB. The IRB Chair or Vice Chair or qualified designee will review all such reports and determine appropriate corrective actions to mitigate further harm to research subjects or others.

Note: Sponsor AE reports that lack meaningful analysis do not constitute adverse events or Unanticipated Problems under this policy.

The IRB must report local unanticipated *serious* adverse events and all Unanticipated Problems to the Institutional Official (IO) for the University's HRPP (at the University, the IO is the Vice President for Research). The IO is responsible for ensuring that such events are reported to the sponsor and all appropriate regulatory and federal agencies as required (45 CFR 46.103.b.5 (DHHS), 21 CFR 56.108(b)(1) (FDA) and VA Handbook 1058.01.

When the University has designated an external IRB to serve as the IRB of Record for University or affiliate research, the external IRB will be responsible for ensuring that all such events are reported to the sponsor, and all appropriate regulatory and federal agencies as described above.

Principal investigators are responsible for informing the sponsor, as described in the funding agreement, of all locally occurring adverse events associated with the use of a drug, whether or not considered drug-related.

Reason for the Policy

The rationale for reporting locally occurring adverse events to the sponsor and the IRB, and Unanticipated Problems to the IRB is to ensure that the research team and the IRB fulfill their obligations to protect human participants. Per federal regulations, the HRPP is required to develop and follow written procedures for insuring prompt reporting of locally occurring serious adverse events to the IRB and sponsor, and of Unanticipated Problems to the IRB.

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (21 CFR 312(a))

Data and Safety Monitoring Board or Committee

A group charged by the sponsor, investigator, or steering committee of a study with protecting subject safety by examining the accruing data for indications of benefit or harm. The Data Safety Monitoring Board (DSMB) or Data Safety Monitoring Committee (DSMC) makes a judgment as to whether the trial should continue. The DSMB or DSMC usually looks at global data, as investigators forward all serious adverse event reports and safety data to a data-coordinating center, which compiles the data for the DSMB or DSMC to review at predefined intervals. Data presented to the DSMB or DSMC are either completely unblinded, or categorized by treatment arm. As such, the DSMB or DSMC is able to determine whether a clear effect exists in one arm of the study versus other arms and to identify trends in increased frequency or severity of anticipated problems.

Human Subject or Human Participant

A living individual

(1) about whom an investigator (whether professional or student) conducting research obtains either

   (a) data through intervention or interaction with the individual;

   (b) identifiable private information; or

(2) who is or becomes a participant in research involving drugs or devices, either as a recipient of a test article or as a control.

Note that both human subject and human participant are used interchangeably in IRB policies and procedures. While the term “participant” conveys the voluntary nature of an individual’s agreement to participate in the research, it also can convey a sense of partnership that is not reflected in all types of research. In some cases, the research volunteer is acted upon more than having any sense of partnership in the research. Hence, the term subject is more appropriate in such cases.

Incidental Finding

A finding concerning an individual research participant that has potential safety, health, psychiatric or reproductive importance that is discovered in the course of research but is beyond the aims of the study. Incidental findings may or may not be anticipated to be found in a portion of the research participants.

IND Safety Reports

Sponsor notifications to FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) of any of the following:

1. serious and unexpected suspected adverse reaction;
2. a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
3. one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug;
4. an aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group;
5. findings from other studies that suggest a significant risk in humans exposed to the drug;
6. findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug; or
7. a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Related Events

These are events that are possibly, probably, or definitely caused by the research procedures or related to research participation.

Serious Adverse Event

Any adverse event that results in any of the following outcomes:

1. death;

2. life-threatening experience;
3. inpatient hospitalization or prolongation of existing hospitalization;
4. persistent or significant disability or incapacity, or congenital anomaly or birth defect;
5. 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.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An incident that is not listed in the investigator brochure or is not listed at the rate of occurrence or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. (FDA)

Unanticipated Problems Involving Risks to Subjects or Others

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the DHHS regulations at 45 CFR part 46. DHHS OHRP considers Unanticipated Problems, in general, to include any incident, experience, or outcome that meets all three of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Other problems that must be reported include

- changes made to the research without prior IRB or EC approval in order to eliminate apparent immediate harm to subjects or others and
- other unanticipated information that is related to the research and indicates that participants or others might be at increased risk of harm.

II2F1 Adverse Events

II2F1a Internal Adverse Events

Reporting Serious Adverse Events to the IRB

Investigators must report to the IRB within five* business days of discovery any internal adverse events that are:

1. serious, unanticipated and associated with the use of a drug in humans whether or not considered to be drug-related; or

2. serious, anticipated and occurring with a greater frequency than expected.

*Internal (local) serious adverse events that are fatal or life-threatening must be reported to the IRB within 48 hours.

Reporting Internal Adverse Events as Unanticipated Problems to the IRB

Upon becoming aware of an internal adverse event, and after determining that the adverse event is not serious, the investigator must assess whether the adverse event represents an Unanticipated Problem as defined above. If the investigator determines that the adverse event represents an Unanticipated Problem (or believes the event *may* constitute an Unanticipated Problem), the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)) (the University, requires such reporting within five days).

Local adverse events that are neither serious nor unexpected, and are occurring at the anticipated rate are to be summarized in the progress report that is submitted at the time of continuing review. The summary may be a simple brief statement that adverse events have occurred at the expected frequency and level of severity as previously documented.

Reporting Internal Adverse Events to the Sponsor

The investigator must report all internal serious or unexpected adverse events, whether determined to be Unanticipated Problems, to a monitoring entity (e.g., sponsor, coordinating or statistical center, independent medical monitor, or Data Safety Monitoring Board or Data Monitoring Committee) as described in the IRB-approved protocol or the contract with the sponsor.

If the investigator determines that an adverse event is not an Unanticipated Problem, but the monitoring entity determines otherwise (for example, due to an unexpectedly higher frequency of the event), the monitoring entity must report this determination to the investigator, and the PI must be promptly report this information to the IRB (45 CFR 46.103(b)(5)).

II2F1b External Adverse Events

University and affiliate investigators participating in multi-center trials will receive numerous reports from the sponsor. When a particular serious adverse event or series of events is determined to meet the criteria of serious, unanticipated and related the PI must report the adverse event as an Unanticipated Problem to the IRB.

Sponsor adverse events reports that are lacking in meaningful analysis are to be summarized in the progress report that is submitted at the time of continuing review.

II2F1c Required Content of Serious Adverse Events Reports

All serious adverse events reports submitted to the IRB must include the following:

- a clear explanation of why the serious adverse event or series of same has been determined to meet the criteria for reporting; and
- a description of any proposed protocol changes or other corrective actions that the investigators have taken or will take to protect the rights and welfare of participants in the research.

II2F2 Unanticipated Problems Involving Risks to Subjects or Others

Unless fatal or life-threatening, investigators must report to the IRB within five days* of discovery of any internal Unanticipated Problems, including incidents, experiences or outcomes that

- are unexpected (in terms of nature, severity, or frequency) given the research procedures and protections described in the protocol and the characteristics of the participant population;
- suggest that the research participation places the participant(s) or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized; and
- are related or possibly related to the participant's involvement in the research.

*Fatal or life-threatening internal Unanticipated Problems must be reported to the IRB within 48 hours of becoming known.

The investigator must include a description of any corrective actions that have been initiated in the conduct of the research to prevent a reoccurrence of the problem or to protect research participants from potential or further harm.

If new information becomes known regarding studies that have closed, expired or been terminated, which may affect former participants or pose new risks to former participants, the principal investigator must notify the IRB of any Unanticipated Problems in order for the IRB to determine whether participants must be informed of the findings.

For multi-site trials, an Unanticipated Problem occurring at an external site must be reported to the IRB only if the report requires changes to the protocol or consent form. While each participating site is required to report an Unanticipated Problem occurring at their site to their IRB and the sponsor in a timely manner, PIs needn't submit to the IRB reports of events from external sites that won't affect the local research or its participants.

II2F3 Adverse Events and Unanticipated Problems in VA Research

Investigators conducting VA research must keep in mind that the definitions of the terms "unanticipated" and "unexpected" include an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

Within five business days of becoming aware of any local (i.e., occurring in the reporting individual's own facility) unanticipated serious adverse events in VA research, members of the VA research community are required to ensure that the serious adverse event has been reported in writing to the IRB.

- This requirement is in addition to other applicable reporting requirements (e.g., reporting to the sponsor under FDA requirements).

The unfounded classification of a serious adverse event as "anticipated" (whether by an investigator or the IRB) constitutes serious non-compliance.

Members of the VA research community, including affiliate investigators conducting VA research, must report to the IRB in writing Unanticipated Problems within five business days of becoming aware of any such problems in VA research.

Unanticipated Problems involving risks to participants or others may include the following:

- interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others;
- any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death;
- any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility's research projects;
- any data monitoring committee, data and safety monitoring board or data and safety monitoring committee report describing a safety problem;
- any sponsor analysis describing a safety problem for which action at the VA facility might be warranted;
- any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; and

- any problem reflecting a deficiency that substantively compromises the effectiveness of the VA facility's HRPP.

If an Unanticipated Problem involves the unauthorized use, loss or disclosure of individually-identifiable patient information, the investigator or the IRB must notify the VASNHCS Privacy Officer within five days of the unauthorized use, loss or disclosure said information.

II2F4 Other Reporting Requirements

Investigators with other regulatory requirements such as the FDA (see Policy I7 Use of Investigational New Drugs and Devices) or contractual reporting requirements related to serious adverse events or Unanticipated Problems (e.g., NIH and study sponsors) are responsible for any reports required under those agreements in addition to the reporting requirement described herein.

II2F4a Clinical Trials of Devices under the IDE Regulations

Adverse Device Effects

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect as "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 relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

Reporting Requirements for Unanticipated Adverse Device Effects

Unanticipated adverse device effects must be reported by the clinical investigator to the sponsor and the reviewing IRB, as follows:

For device studies, investigators are required to submit a report of an unanticipated adverse device effect to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)).

Sponsors must immediately conduct an evaluation of the investigator's report of an unanticipated adverse device effect and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b) and 812.150(b)(1)).

The IDE regulations require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of Unanticipated Problems under the IND regulations.

II2F5 IRB Response to Reports

The IRB Chair, Vice Chair or Program Manager; or other qualified designee will evaluate the reported event in accordance with IRB Procedure II2F PR3 and will determine if the event report requires review at a convened meeting.

The IRB Chair or Vice Chair, or other qualified designee will determine whether further, immediate corrective actions are needed to protect the subjects, and if subjects should be notified. The IRB will provide the investigator with notification of this determination in writing.

The IRB Chair, Vice Chair or Program Manager; or other qualified designee will initially assess whether or not an adverse event or Unanticipated Problem involves, or has the potential to involve, risk of harm to subjects or others. If this assessment indicates that a local event is serious, and unanticipated or exceeds the frequency of occurrence of severity of symptoms initially anticipated in the research; or may constitute an Unanticipated Problem, the IRB will provide a report to the IO. If upon completion of this initial review, the IRB determines an incident is likely to constitute an Unanticipated Problem involving risks to subjects or others, the IRB may provide a preliminary report to the federal Office of Human Research Protections (if applicable).

The IO after consultation with the IRB, will report to the federal Office of Human Research Protections (if applicable) any incident that the IRB has determined constitutes an unanticipated serious adverse event related to research participation or an Unanticipated Problem involving risks to subjects or others. Reporting by the IO is not required if the event is known to have been reported by other means, such as by the study sponsor.

II2F5a IRB Review and Response to Reportable Events for VA Research

Within five business days after receiving a report of a local unanticipated serious adverse event or Unanticipated Problem, the IRB Chair or Vice Chair or other qualified IRB member-reviewer; or the convened IRB must determine and document whether the reported incident was serious, unanticipated and related to the research. “Related” means the event or problem may reasonably be regarded as caused by, or probably caused by, the research.

If the IRB Chair, Vice Chair or member-reviewer; or convened IRB determines that the problem or event was serious, unanticipated, and related to the research, within five business days of the determination the IRB Chair or designee must report the serious adverse event or Unanticipated Problem in writing to the

- Medical Center Director,
- Associate Chief of Staff for Research, and
- Research and Development Committee.

If the IRB Chair, Vice Chair or member-reviewer; or convened IRB determines that the problem or event was serious, unanticipated, and related to the research, a simultaneous determination is required

regarding the need for any action (e.g., suspension of activities; notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations.

All determinations of the IRB reviewer when made outside of a convened IRB meeting (regardless of outcome) must be reported to the IRB at its next convened meeting. If the IRB reviewer determined that the problem or event was serious, unanticipated and related to the research, the convened IRB must determine and document whether a protocol or consent document modification is warranted.

If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document

- whether previously enrolled subjects must be notified of the modification, and if so,
- when such notification must take place and how such notification must be documented.

See IRB procedure IIF PR3 for IRB reporting requirements for Unanticipated Problems in VA Research.