



Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 1 of 11

Human Research Protection Program Procedure

REVIEW OF REPORTABLE EVENTS

DESCRIPTION

The Principal Investigator will report unanticipated problems involving risks to participants or others to the Institutional Review Board so that they may be investigated and action taken to protect research participants and others. Reportable events include unanticipated problems involving risk to participants or others, adverse events and other problems. The IRB will identify a member or members with expertise in the research to investigate the deviation, unanticipated problem or adverse event to determine whether the event involves risks to participants or others.

RESPONSIBILITY

The IRB Chair or designee, designated IRB members and the IRB at a convened meeting are responsible for review and evaluation of unanticipated problems and protocol deviations. In appropriate cases, the problem and its resolution may be reported to regulatory and funding agencies by the Associate Vice President (AVP) and Institutional Official (IO) as well as to the VA Research and Development Office, if appropriate.

DEFINITIONS

Types of Study Events

- 1. Unanticipated problem involving risk to subjects or others** – Any problems which were not contemplated when the research was approved and which present risk of serious harm to subjects or to others, including the research team, the university community, or the broader community. Unanticipated problems (UPs) are always related to an approved study, either ongoing or closed.

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

- 1.** Unexpected (in terms of nature, severity, or frequency) given that the research procedures that are described in the protocol-related documents, and informed consent document, or the Investigator Brochure; and (b) the characteristics of the subject population being studied; and

Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 2 of 11

2. Suggests that the research places the subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The following problems/events represent unanticipated problems involving risks to participants or others. This list is not exhaustive.

- Information that indicates a change to the risks of potential benefits of the research, in terms of severity or frequency. For example:
 - An interim analysis indicates that participants have a lower rate of response to treatment than was initially expected.
 - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
 - A paper is published from another study that shows that an arm of the research study is of no therapeutic value.
- Any adverse event that represents a serious unexpected problem that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- Adverse event that would cause the sponsor to modify the investigator's brochure, protocol, or informed consent to assure the protection of human subjects.
- A change in FDA labeling or FDA withdrawal from marketing for safety concerns of a drug, device, or biologic used in a research protocol.
- Change to the protocol taken without prior IRB review to eliminate the apparent immediate hazard to a research participant.

Other Reportable Events

- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Violation, meaning an accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk or has the potential to occur again.
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the participant to remain in the study.

The IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event presenting risk to the participant.

Human Research Protection
Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 3 of 11

2. **Unanticipated Adverse Device Effect:** 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 or 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.
3. **Adverse Events (AE):** “any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research”

The event is undesirable and has an unintended outcome, but is not necessarily unexpected. The event may have been described in the informed consent as a risk of the study. Adverse events include abnormal laboratory findings, a symptom, or disease temporally associated with the use of an investigational agent, or the progression of disease, whether or not related to the medicinal (investigational) product.

Serious Adverse Event (SAE): The events listed are examples and are not limited to the following:

- The death of a study subject, whether related to an investigational agent or not related
- A reaction which, in the opinion of the investigator, threatens the study subject with risk of death
- A disability or incapacity which, in the opinion of the investigator, causes substantial disruption of a study subject's ability to conduct normal life functions
- Hospitalization or extension of an existing hospitalization (excluding elective hospitalization for conditions unrelated to the study)
- A birth defect in an offspring of a study participant, regardless of the time after the study the congenital defect is diagnosed
- Any intervention required to prevent one of the above outcomes

Note: drug overdose and cancer have been removed from the list of adverse events that are characterized as SERIOUS (unless the overdose or cancer meets the above criteria).

Related Adverse Event: - The adverse event could have been caused by any drug given to a subject as part of the study, a device used in the study, or a procedure that is carried out as part of the study. The term “adverse drug reaction” (ADR) is also used if the AE or SAE is related to the investigational product.

Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 4 of 11

Unexpected Adverse Event: -the adverse event is not an anticipated event for the study drug, device, or procedure and is not explained in the Informed Consent Statement that the study subject signed.

Imminent Threat of an AE in Research – Any situation in which an AE in research has not yet occurred but is very likely to occur without preventative measures (VA term)

Unexpected Death: The death of a research participant in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention definitely, probably or possibly hastened the participant's death. A participant's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of these procedures.

3. Protocol Deviations –

Significant Deviations – Accidental or unintentional change to the IRB approved protocol may be considered a failure to protect the rights, safety and welfare of participants because the non-compliance exposes participants to unreasonable risks. The listed deviations are examples and are not limited to the following:

- Failure to adhere to the inclusion/exclusion criteria that are specifically intended to exclude participants for whom the study drug or device poses unreasonable risks (e.g., enrolling a participant with decreased renal function in a research study in which decreased function is exclusionary because the drug may be nephrotoxic)
- Failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that causes neutropenia)

Deviations unlikely to place one or more participants at risk or have the potential to occur again, may be reported to the IRB using the Deviation Report Form located on the IRB website.

Subject Non-Compliance – Subject non-compliance occurs when, despite the best efforts of the research staff, the subject fails to follow the protocol Note that failure of the research staff should not be classified as Subject Non-Compliance (ex. the subject did not complete a six-month telephone follow-up because a staff member forgot to call). Also note that Subject Non-Compliance may become a Significant Deviation if it occurs in a significant number of subjects. Subject Non-Compliance may also be considered a Safety Violation (ex. the subject takes medication that is contraindicated by the study drug).

Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 5 of 11

4. Complaints - an expression of dissatisfaction or concern about safety, privacy or protection of a subject regarding human subject research.

- **Minor complaint** – a complaint that alleges an inconvenience to human participants but does not result in an unanticipated problem or serious adverse event or increase in risk. Examples are questions about the amount of participant payment; no close parking available; study personnel were rude; incorrect form was used.
- **Major complaint** – a complaint that alleges that human participants are being put at risk or increased risk compared with what is described in the consent form. Examples are PI not allowing enough time for the consent process; PI not following inclusion/exclusion criteria; failure to follow protocol; failure to report unanticipated problems or SAEs; participant feels like their rights have been violated; PI not complying with Human Research Protection Program (HRPP) policies or federal regulations; a series of minor complaints.

Additional terms relevant to this policy

Relatedness

- **Related:** Associated or having a timely relationship with the study agent or procedures; a reasonable possibility exists that an outcome may have been caused or influenced by the study in question (e.g., administration of a study drug, devices or procedures), although an alternative cause/influence may also be present. Related events may be *definitely, probably, or possibly* related.
- **Unrelated:** Unassociated or without a timely relationship to the study agent or procedures; evidence exists that an outcome is definitely related to a cause other than the event in question (e.g., underlying disease, environment).

Location

Internal: An event occurring in research at University of Cincinnati (UC), sites affiliated with UC or at a site(s) under an UC IRB's jurisdiction.

External: An event occurring in research at a site(s) other than UC, over which another (non-UC) IRB has jurisdiction.



Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 6 of 11

ADVERSE EVENT REVIEW PROCESS

1. Principal Investigators will submit all unanticipated problems involving risk to participants or others, adverse events and other problems, occurring to participants in studies conducted at the institution's facilities as described in Policy II.02.
2. The IRB will accept non-site adverse event reports (IND safety reports), SUSAR reports, etc., submitted by investigators and sponsors on behalf of the investigators if in accord with federal regulations.
 - the event is both serious and unexpected
 - the report identifies all previous safety reports concerning similar adverse experiences
 - the report analyzes the significance of the current adverse experience in light of the previous reports, **and**
 - the report outlines a corrective action plan.
3. The IRB Chair, Vice-Chair or IRB member designated by the Chair will review all adverse event reports submitted to determine whether they are serious adverse events and whether they are unanticipated problems involving risks to participants or others.
4. If it is determined that the adverse event was serious or unexpected or an unanticipated problem involving risks to participants or others. These will be reviewed by the convened IRB.
5. All serious or unexpected adverse events will be reviewed within 10 working days of receipt.

For VA conducted research: Within 5 business days after a report of a serious unanticipated problem involving risks to subjects or others, or of a local unanticipated SAE, the convened IRB or qualified IRB member-reviewer must determine and document whether or not the reported incident was serious, unanticipated, and related (related meaning the event or problem may reasonably be regarded as caused by, or probably caused by, the research) to the research.

If the convened IRB or the qualified IRB member-reviewer determines that the problem or event is serious and unanticipated and related to the research, the IRB Chair or designee must notify the Office of Research Oversight (ORO) via telephone or email within 48 hours and report the problem or event directly (without intermediaries) to the facility director within 5 business days after the determination. The report to the director must be made in writing, with simultaneous copy to the Associate Chief of Staff (ACOS) for Research and the Research and Development (R&D Committee).

If the convened IRB or the qualified IRB member-reviewer 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;



Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 7 of 11

notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations in 38 CFR 16.103(b)(4)(iii).

All determinations of the qualified IRB member-review (regardless of outcome) must be reported to the IRB at its next convened meeting.

If it was determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether or not a protocol or informed consent modification is warranted.

If the convened IRB determines that a protocol or informed consent modification is warranted, the IRB must also determine and document the following: (a) Whether or not previously enrolled subjects must be notified of the modification and if so, (b) When such notification must take place and how such notification must be documented.

6. If the event is determined to be an unanticipated problem involving risk to participants or others, it will be handled in accordance with Policy II.02, *Reporting to the IRB Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems*.
7. Questions to be considered when reviewing an event:
 - a. Date and time of onset of adverse event.
 - b. Was the event/problem from this institution, or another participating site if a multi-center sponsor or study?
 - c. Was the event/problem deemed mild, moderate, severe, or fatal? If fatal, date of death, including copy of the death certificate and autopsy report should be obtained.
 - d. Was the event/problem expected or unexpected?
 - e. Was the event/problem related to the research intervention?
 - f. Determine if the event was study related.
 - g. What was the outcome? Is it resolved, ongoing or did the participant die?
 - h. Based on this event, will additional monitoring of other patients be performed in the study to detect similar problems early? If yes, please describe.
 - i. Are the possibility, severity and specificity of this event described in the consent form, protocol, and investigator brochure for this study?
 - j. Will the consent procedures be revised as a result of this event? If yes, attach the new version of the consent form.
 - k. Will patients already enrolled in the study be informed about the possibility of this adverse event? If yes, how? Attach all appropriate documents.



Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 8 of 11

The reviewer shall report on the following to the IRB at a convened meeting:

1. Additional risks that may need to be included in the risk section of the consent form.
2. An increase in risks that may indicate the need to halt study enrollment; close the study entirely; or modify the study design.
3. If the reviewer (or the Committee) feel it necessary to supplement their review, they may request an outside "expert" to review and comment
4. Approval of the description and reporting of the adverse event.

UNANTICIPATED PROBLEMS AND PROTOCOL DEVIATION REVIEW PROCESS

Any IRB member or HRPP staff may become aware of an unanticipated problem or a protocol deviation through a report by a participant, investigator, news article, personal involvement or other means. Any report of an unanticipated problem will be brought to the attention of the IRB Chair who will determine whether it was an unanticipated problem involving risks to Participants or Others.

1. The IRB Chair or designee will investigate to determine whether the problem was an unanticipated problem involving risks to participants and others. If the investigation finds that it is an unanticipated problem, the IRB Chair or designee will prepare a report to present to the IRB for review and action.
2. The report will include at least
 - a. The PI and research staff member involved,
 - b. The time and place of the problem,
 - c. The events that took place,
 - d. The records reviewed,
 - e. The persons interviewed, if any,
 - f. The harm or potential harm presented by the problem
 - g. The action, if any, taken by the PI or research staff to treat, assist, or make restitution to any participant or other individual who has been harmed.
 - h. The action, if any, taken by the PI or research staff to correct or prevent the problem
 - i. A recommended corrective action, if needed,
 - j. Any other information relevant to the problem.
3. The report will be presented at a convened meeting of the IRB. The PI will receive a copy of the report and will be invited to attend the IRB meeting at which the report discussed to present information and answer questions. After reviewing and

Human Research Protection Program Procedure

Procedure Number: 320

Review of Reportable Events

Adopted: 11/2005

Revised: 06/2014

Page: 9 of 11

discussing the report and the PI has been excused, the IRB may take any action it believes appropriate, including the following:

- a. Acknowledgement in the research protocol IRB file that the event occurred and that no harm was done and no further action was required.
 - b. Requirement to modify the procedures and/or consent, including a decision to reconsent participants in the study.
 - c. Requirement to make restitution to individuals who experienced the problem.
 - d. Suspension or termination of the research with reasons communicated to the principal investigator by the IRB chair.
 - e. Any other action appropriate to ensure the safety and welfare of participants and others and the ethical conduct of research.
4. The action of the IRB will be reported to the AVP and IO who will send the report and action taken to OHRP, if the research is a DHHS-funded study.

All deviations will be reviewed by the appropriate IRB Chair or designee.

1. He or she will evaluate these deviations to determine if there is a pattern of conducting the study outside its written limitations.
2. If a pattern appears to exist, the IRB Chair may request additional information from the local study site to understand the context in which these deviations have occurred.
3. The IRB Chair may then notify the full IRB for further action. Further action may include discussion with or retraining of the local site personnel and/or referral to the UC Compliance Monitoring Department.

ACTIONS OF THE IRB

Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- 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
- provision of additional information about newly recognized risks to previously enrolled subjects.



Human Research Protection
Program Procedure

Procedure Number: 320
Review of Reportable Events
Adopted: 11/2005 Revised: 06/2014
Page: 10 of 11

If new or increased risks are determined, the IRB may request in writing that the PI add additional risks to the protocol or consent/assent forms. Changes to the consent/assent must take into consideration both prospective participants and participants already enrolled in the study. If the change might affect the participant's decision to remain in the study, the participant/parents must be re-consented using the revised consent/assent forms. The revised consent/assent forms will be approved and date stamped by the IRB.

The IRB may suspend or terminate research if the information gained during its review of the adverse events indicates that human participants in a research project are exposed to unexpected serious harm. When such action occurs, the IRB will provide a statement of action to the investigator, and the Institutional Official or designee will notify the sponsor and governing regulatory authority in writing of all protocols suspended for cause. This notification will include the reason for suspension and the action taken to resolve the issue.

The IRB may accept the findings of the PI and designated reviewers. The AE report will be placed in the protocol file and reported during continuing review.

Applicable Regulations, Document(s):

21 CFR 56.108(b)

45 CFR 46.103(b)(5)

38 CFR 16.103(b)(5)(1)(i)

21 CFR 312.32

21 CFR 812.60-66: 812.150

Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection, DHHS, FDA, January 2009

HRPP Policy II.02 Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems

HRPP Policy VII.02 Reporting of Unanticipated Problems, Non-Compliance, Suspensions and Terminations to the Appropriate Institutional Officials, Departments and Agencies

HRPP Policy VII.03 Investigating Allegations of Non-Compliance in Human Subjects Research

Event Reporting Form for Unanticipated Problems Involving Risks to Participants or Others, Adverse Events, and Other Problems

Adoption Date:	Created by:	Date of Revision:	Revised By:	Summary of Revision:
11/2005	C. Fabby	07/2007	D. Oneill	Updated IRB office staff terminology.



Human Research Protection
Program Procedure

Procedure Number: 320
Review of Reportable Events
Adopted: 11/2005 Revised: 06/2014
Page: 11 of 11

05/2008	M. Linke	05/2008	J. Gerlach	Updated procedure to incorporate IRB-S. Updated review of unanticipated problems and protocol deviations to have review conducted by IRB Chair or designee.
		07/2009	M. Linke	Update procedure to incorporate FDA Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs- Involving Human Subject Protection, January 2009. Definitions updated to reflect HRPP Policy II.02
		08/2010	J.Gerlach	Added text regarding time for IRB review of VAMC reported unanticipated events, Revised text regarding examples of unanticipated events, added UADE, Added references to 21 CFR 812 and 21 CFR 312.
		1/2013	J. Osborne	Revised language for VA requirements on pages 6-7
		6/2014	A Braggs-Brown	Revised to reflect organizational changes

Date Adopted: June 2014 **Signature signed copy on file**