

**IRB Policy 18: Reporting of Unanticipated Problems/Events**  
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**6/11/10, revised January 27, 2011, revised January 17,**  
**2012, revised 9/17/15**

**I. Pertinent Definitions:**

**Unanticipated Problem Involving Risks to Subjects or Others**

**(UPIRTSO):** Includes those events that (1) are not expected given the nature of the research procedures and the subject population being studied (2) suggest that the research places subjects or others at a greater risk of harm or discomfort related to the research than was previously known or recognized and (3) are related or possibly related to the research.

Possibly related: there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected: unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document and given the characteristics of the subject population being studied

**Serious Adverse Event:** any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For VA studies, a

Serious Adverse Event (SAE) is an untoward occurrence in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect, or that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome.

**Unexpected Adverse Event:** As defined by the FDA, any adverse event, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure only listed cerebral vascular accidents. **Clarification Note:** “Unexpected,” as used in this definition, refers to an adverse event that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product and not listed in the Investigator’s Brochure.

Unexpected adverse event: any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is NOT consistent with either (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved consent document and (b) other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

For VA studies,

Unanticipated and unexpected refer to an event or problem in human research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol documents and the characteristics of the study population.

**Serious Problem.** A serious problem is a problem in human research or research information security that may reasonably be regarded as:

- (1) Presenting a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research personnel, or others, including their rights to privacy and confidentiality of identifiable private information; or
- (2) Substantively compromising a facility’s HRPP or research information security program.

## **II. Summary Policy**

Federal regulations require the organization to ensure prompt reporting of “any unanticipated problems involving risk to subjects or others” to the IRB, regulatory agencies, and institutional officials.

For non-VA studies, the ETSU/VA and ETSU IRB require investigators to promptly submit any problem or event that meets the following criteria to the IRB within 10 working days using the Form 109 (unanticipated problem report) signed by the PI.

For VA studies, VA reporting requirements require immediate reporting of the loss, unauthorized use, disclosure, transmission, removal, theft, or destruction of VA research related PHI or confidential information stored on portable media such as laptops or personal computers- see Section V. VA reporting requirements require Investigators, VA Research Compliance Officers, and other members of the VA research community to report all problems involving, or suggesting, risks to subjects or others in VA Research to the Associate Chief of Staff for Research (ACOS/R) which is internal reporting and to the ETSU/VA IRB as soon as possible but no later than five business days after becoming aware of the problem which is external reporting. The IRB may determine that additional external reporting may be warranted to include reporting to the Office of Research and Development (ORD), the Office of Research Oversight (ORO), the Office of Human Research Protections (OHRP) and the Food and Drug Administration (FDA).

Events to be reported include:

- a. any event, including on-site and off-site adverse events, injuries, side effects, deaths, or other problems, which in the opinion of the local PI, was unexpected, suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized, and was related to or possibly related to the research.\*
- b. accidental or unintentional change to the IRB approved protocol that involves the potential for increased risk
- c. Any deviation from the protocol taken without IRB approval to eliminate apparent immediate hazard to a research participant
- d. Any publication in the literature, safety monitoring report,(including Data and Safety Monitoring Reports), interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
- e. Any breach in confidentiality that may involve risk to the participant or others
- f. Any complaint of a participant that indicates an unanticipated risk or that cannot be resolved by the research staff
- g. any local death, whether anticipated or not\*
- h. incarceration of a participant
- i. Any other possibly related event which in the opinion of the investigator constitutes an unanticipated risk.

- j. Addition of a black box warning on any drug used in your research (for VA studies, this also includes VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to a VA research study
- k. interruptions of subject enrollment or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff. or others.\*\*
- l. Any work-related injury to personnel involved in human research, or any research-related injury to any other person, requiring more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or that leads to serious complication or death.
- m. Any Data Monitoring Committee (DMC) report or any sponsor analysis describing a safety problem
- n. For VA studies, any local Serious Adverse Event that is both unanticipated and related to the research  
(see definition)
- o., 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
- p. For VA studies, any problem reflecting a deficiency that substantially compromises the effectiveness of the institution's human research protection or human research oversight programs.
- q. For VA studies, any serious problem that is both unanticipated and related to the research.

\*For VA studies, the following apply to a local research death that is both unanticipated and related to the research. :

1. VA personnel, including WOC and IPA appointees, must ensure oral notification of the Institutional Review Board (IRB) immediately upon becoming aware of any local research death that is both unanticipated and related to the research.
2. The IRB must alert ORO by e-mail or telephone within 2 business days after receiving such notification and provide relevant information as requested. The VA facility Director and the ACOS/R&D must receive concurrent notification.
3. VA personnel, including WOC and IPA appointees, must ensure written notification of the IRB within 5 business days of becoming aware of the death.
4. Within 5 business days after receiving written notification of the death, the IRB Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.
5. The IRB must review the death and the determination of the IRB Chair or qualified IRB member-reviewer at its next convened meeting and must determine and document that:
  - (a) The death was both unanticipated and related to the research; or
  - (b) There is insufficient information to determine whether the death was both unanticipated and related to the research; or

(c) The death was not unanticipated and/or the death was not related to the research.

6. Regardless of the determination under paragraph above, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.
7. The IRB must notify the VA facility Director and the ACOS/R&D of its determinations under sections 5 and 6 within 5 business days of the determinations.
8. The VA facility Director must report the determinations to ORO within 5 business days after receiving the IRB's notification.

\*\* For VA studies, when receiving a report of a suspension or termination of VA research, the convened IRB must review the suspension/termination at the earliest practicable opportunity, not to exceed 30 business days after notification, to determine whether it:

- (a) Resulted from a local adverse event(s), local noncompliance, or other local issue(s); or
- (b) Requires local action (in addition to the suspension/termination) to ensure the safety, rights, or welfare of local human research subjects, personnel, or others or the effectiveness of the local HRPP.

(2) If the IRB determines that either (a) or (b) above applies,

(a) The IRB must notify the VA facility Director and the ACOS/R&D within 5 business days after the determination;

(b) The VA facility Director must report the suspension/termination to ORO within 5 business days after receiving the IRB's notification.

### III. **Non-VA** PI Responsibilities regarding Adverse Event Assessment (category a above) SEE SECTION IV for VA studies

#### A. Internal adverse events

Upon becoming aware of an internal adverse event, PIs are required to promptly assess the event and determine whether the event is a UPIRTSO. PIs must evaluate each event by the following three criteria in order to make that determination.

If the answer to the three following questions is "yes", then the event is a UPIRTSO and must be submitted to the IRB within 10 working days using the Form 109.

1. Is the adverse event unexpected?
2. Is the adverse event related or possibly related to participation in the research?
3. Does the adverse event suggest that the research places subjects or others

at a greater risk of harm than was previously known or recognized? \*

\*Note: If the adverse event is serious (see definition above), the answer to this question is always “yes”.

If the answer to all three questions is “yes” then the event meets the definition of a UPIRTSO and must be reported to the IRB within 10 working days on a form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event’s impact on the risk-potential benefit profile of the study.

If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 10 days but is reportable to the IRB in summary format at the time of continuing review.

Regardless of the determination, PIs also are responsible for ensuring that the adverse event is reported to the monitoring entity if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

## B. External adverse events

When PIs receive a report of an external adverse event, PIs are required to promptly assess the event and determine whether the event is a UPIRTSO. Only external adverse events that are identified as meeting the three criteria above must be reported promptly to the IRB as UPIRTSOs. If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 10 days but is reportable to the IRB in summary format at the time of continuing review. If all three questions are answered “yes”, then the PI must within 10 days submit BOTH a form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event’s impact on the risk-potential benefit profile of the study.

Reports of off-site events occurring in studies that are completed and closed at the local site should be reported if the event meets the IRB definition as detailed above AND the local PI judges that this event may affect risk to participants who have completed the study.

Follow-up reports of an off-site event may be submitted on a tracking log without an accompanying Form 109 if the following are true:

1. the initial report of the event was submitted as a UPIRTSO on a Form 109
2. the local PI has determined that the follow-up information does not contribute meaningful new information

All problems/events that do not meet these criteria should be reported to the IRB in summary form (table or spreadsheet) at the time of continuing review.

#### IV. **VA** PI Responsibilities regarding Adverse Event Assessment (category a above)

##### A. Internal adverse events

Upon becoming aware of an internal adverse event, PIs are required to promptly assess the event and make 2 determinations.

1. Is the event a local SAE that is both unanticipated and related to the research ? (see definition in Section I)

If the event is a local SAE that is both unanticipated and related to the research, the PI must report the event to the ACOS for R and the ETSU/VA IRB using xform 109 as soon as possible, but no later than 5 business days after the event has become known to the investigator.

2.If the event is not a local SAE that is both unanticipated and related to the research, the PI must evaluate each event by the following three criteria in order to determine whether the event is a UPIRTSO.

If the answer to the three following questions is “yes”, then the event is a UPIRTSO and must be submitted to the IRB within 5 business days using the Form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event’s impact on the risk-potential benefit profile of the study.

1. Is the adverse event unexpected?
2. Is the adverse event related or possibly related to participation in the research?
3. Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 5 days but is reportable to the IRB in summary format at the time of continuing review. Regardless of the determination, PIs also are responsible for ensuring that the adverse event is reported to the monitoring entity if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

For VA researchers, the unfounded classification of a serious adverse event as “anticipated” constitutes serious non-compliance.

##### B. External adverse events

When PIs receive a report of an external adverse event, PIs are required to promptly assess the event and determine whether the event is a UPIRTSO. Only external adverse events that are identified as meeting the three criteria above must be reported

promptly to the IRB as UPIRTSOs. If all three questions are not answered “yes”, then the event does not meet the definition of a UPIRTSO. The event is not required to be reported to the IRB within 5 days but is reportable to the IRB in summary format at the time of continuing review. If all three questions are answered “yes”, then the PI must within 5 business days submit BOTH a form 109 and a modification request. The modification request must outline the necessary revisions to the IRB approved protocol, consent document or other associated documents to incorporate the event’s impact on the risk-potential benefit profile of the study.

Reports of off-site events occurring in studies that are completed and closed at the local site should be reported if the event meets the IRB definition as detailed above AND the local PI judges that this event may affect risk to participants who have completed the study.

Follow-up reports of an off-site event may be submitted on a tracking log without an accompanying Form 109 if the following are true:

4. the initial report of the event was submitted as a UPIRTSO on a Form 109
5. the local PI has determined that the follow-up information does not contribute meaningful new information

All problems/events that do not meet these criteria should be reported to the IRB in summary form (table or spreadsheet) at the time of continuing review.

## **V. \*VA Reporting of Loss or Theft of VA research data/information**

VA reporting requirements require immediate reporting of the loss, unauthorized use, disclosure, transmission, removal, theft, or destruction of VA research related PHI or confidential information stored on portable media such as laptops or personal

computers-

1. Report the loss to security/ police officers IMMEDIATELY. If within a VA health care facility, notify the VA police. If the loss or theft occurs while on travel or at another institution, notify the security police officers at the institution (such as hotel security, university security, etc.) as well as the police in the jurisdiction where the event occurred.
2. Obtain the case number and the name and badge number of the investigating officer. If possible, a copy of the case report should be obtained.
3. Report the incident within one hour to

- your immediate supervisor\*
- VA Privacy Officer at your facility \*
- VA Information Security Officer at your facility\*
- ACOS/R at your facility\*

4. Report the incident to the IRB using a xForm 109 (Unanticipated Problem Involving Risks to Subjects or Others).

\* The name and contact information should always be readily available. Wallet cards that list the contact name and number of the James H. Quillen VA ACOS/R, the VAMC Privacy Officer and the VAMC Information Security Officer are available through the VAMC R&D office and the IRB Office.

The ACOS/R&D must immediately notify the IRB.

## **VI. IRB Responsibilities**

The IRB Coordinator will present the written report of the unanticipated event received from the investigator to the IRB Chair within 5 days.\* (SEE EXCEPTION BELOW FOR VA STUDIES). For VA reports of a local SAE or a serious problem that is both unanticipated and related to the research, the IRB Chair must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects within 5 business days after the IRB receiving the written notification .

The Chair will perform an initial review, and determine whether the event is an unanticipated problem involving risks to participants or others. In addition, for VA studies, the Chair will determine and document on the UPIRTSO Reviewer Form whether the problem or local SAE is serious, unanticipated, or related or possibly related. The Chair determines the action required based on his/her decision. If the Chair determines that the event is not a UPIRTSO, no further action is taken. If the Chair determines that the event is a UPIRTSO, the Chair will consider suspension or other immediate action such as notification of participants and refer the report to the IRB. If the Chair determines that there is the potential of immediate harm to participants, the Chair may immediately suspend the study pending the IRB's receipt and review of the unanticipated problem and determination of any required actions.

If Chair determines that the report is a UPIRTSO, the report, with any attached documents, the narrative description of the project, and the current approved informed consent, will be forwarded to the IRB Primary Unanticipated Problem (UP) Reviewer for initial review. The UP Reviewer, appointed by the IRB, will review all UPIRTSOs submitted and report findings and any recommendations for local ICD revisions to the IRB. In addition, all IRB members receive a copy of the Unanticipated Event Form (xForm 109), the narrative description of the project, and the currently approved consent document. If additional information is required in order to make a final determination concerning the event, the investigator will receive such a request in writing from the Chair/Board. The report will be added to the next agenda for the convened board. VA events requiring review by the convened board must be reviewed at the IRB's next convened meeting.

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For VA studies, the IRB must review the incident and the determination of the IRB Chair or qualified IRB member-reviewer at its next convened meeting and must determine and document that:

- (a) The incident was serious and unanticipated and related to the research; or
- (b) There is insufficient information to determine whether the incident was serious and unanticipated and related to the research; or
- (c) The incident was not serious, and/or the incident was not unanticipated, and/or the incident was not related to the research.

Regardless of the determination above, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether or not investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.

For VA studies, notifications of information security incidents must be reviewed by the IRB at its earliest practicable convened meeting, not to exceed 30 business days from the date of notification.

1. The IRB must determine:

- (a) Whether or not the incident constitutes a serious problem and
- (b) In conjunction with the ISO and/or PO as applicable, whether and what remedial actions are warranted by the facility or the relevant investigator(s).

2. If the IRB determines that the incident constitutes a serious problem:

- (a) The committee must notify the VA facility Director and the ACOS/R&D within 5 business days after the determination.
- (b) The VA facility Director must report the determination to ORO within 5 business days after receiving the committee's notification.

(3) If the IRB makes additional determinations under its authority (e.g., if the IRB determines that the incident also involves serious noncompliance with human research protection requirements), any reporting requirements pertinent to such determinations must also be satisfied.

Refer to Policy 34 for VA reporting requirements.

Examples of corrective actions or substantive changes that might need to be considered by the IRB in response to a UPIRTSO include:

- a. Modification of inclusion or exclusion criteria to mitigate the newly identified risk
- b. Implementation of additional procedures for monitoring subjects
- c. Suspension of enrollment of new subjects
- d. Suspension of research procedures in currently enrolled subjects

- e. Modification of informed consent documents to include a description of newly recognized risks
- f. Provision of additional information about newly recognized risks to previously enrolled subjects (if IRB determines that an informed consent modification is warranted, the convened IRB must determine and document in the minutes whether or not previously enrolled subjects must be notified of the modification and if so, when such modification must take place and how such notification must be documented)
- g. Reconsideration of study approval
- h. Revision of the continuing review timetable
- i. Requirement of notification of past participants

The IRB may deem it necessary to directly audit the research site and medical records pertaining to the event, monitor the consent process, interview participants or witnesses, or suspend/withdraw IRB approval until such time that the safety of the participants can be assured. If information that may relate to subject's willingness to continue to take part in the research is noted, the IRB will require notification of current participants. The IRB may require that current participants be re-consented. The IRB may terminate 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: (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.

Correspondence will be forwarded to the Principal Investigator as per the decision of the IRB following the completion of the review process.

If the Chair determines the event is a UPIRTSO, the reporting requirements outlined in Policy 34 will be followed.

The ETSU/VA IRB Chair is responsible for reviewing any report of a local death to determine if the death is unanticipated. For VA studies, if the Chair determines that the death is unanticipated, the ETSU/VA IRB Coordinator immediately forwards the Chair's written assessment to the VA AO.

If the local site submits a tracking log for non-reportable events to satisfy sponsor requirements, the events/problems listed on the tracking log will be acknowledged by the IRB Chair, as indicated by his/her initials and date in the final column of the tracking log. A copy of the log will be filed with the study file, and the original returned to the investigator.

\*For VA studies,

If the IRB receives a report of a reported loss or theft of VA research data/information or portable media, the report will be immediately forwarded to the HRPP Director. The HRPP Director will immediately follow the reporting pathway outlined in Section III above.

#### References

45 CFR 46. 103(b)(4)(iii)

21 CFR 56.108(b)(1)

OHRP Compliance

45 CFR 46 104(a)

45 CFR 35 104 (b)

VHA Handbook 1058.1

Appendix A, Memo from Deputy Under Secretary for Health Operations and Management (DUSHOM) and Chief Research and Development Officer (CRADO) dated February 6, 2007

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events dated January 15, 2007

VHA Handbook 1058.01 June 15, 2015