

Stratton VA Medical Center

IRB Standard Operating Procedure: Reporting of Adverse Events & Unanticipated Problems

DEFINITIONS

- **Adverse Event (AE)** - Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.
- **Serious Adverse Event (SAE)** – Any Adverse Event that results in death, a life-threatening situation, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability, a birth defect, and other events that may not result in death, be life-threatening, or require hospitalization but which require medical intervention to prevent one of the outcomes listed above.
- **Unanticipated Problem (UP) related to Subjects or others:** any incident, experience, or outcome that meets **all** 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 anticipated.

PROCEDURE SUMMARY

All protocols when initially approved by the IRB must include a section relating to the procedures the PI will follow in relation to reporting and handling of adverse events and unanticipated problems involving risks to subjects or others. These provisions may include a Data Safety Monitoring Board (DSMB) and a plan for reporting DSMB findings to the IRB.

DETERMINATION OF REPORTING REQUIREMENTS AND RELATED PROCEDURES

AE Reporting of Internal or Local AEs:

The principal investigator (PI) must determine whether internal or local AEs are anticipated or not. Only unanticipated AEs will be considered for reporting.

For minimal risk studies, the PI must also determine if an unanticipated AE is serious. If not serious, the AE need not be reported. If serious, the AE must be reported by the PI to the IRB within three (3) business days of the awareness of the occurrence via the Research Program office or an IRB member.

For moderate to high risk studies, the PI must report all unanticipated AEs to the IRB within three (3) days of awareness of the occurrence through the Research Program office or an IRB member. An IRB voting member-reviewer or alternatively, the convened IRB must determine whether this category of AEs is serious or not. If determined to be not serious, then no additional reporting is required. If they are determined to be serious, further reporting, as described below, must be done.

For both minimal risk and moderate to high-risk studies, with AEs identified as local, unanticipated and serious, the IRB must discuss and evaluate whether the AEs are related, possibly related or probably related to the research in accordance with VHA Handbook (ORO) 1058.01.

Reporting Required of the PI for Onsite Adverse Events for Moderate to High Risk Studies

Documents to be submitted by the PI are to include the Stratton VAMC AE/UP report form and the following documents as appropriate:

- All documentation received from the sponsor such as safety reports, FDA Med Watch reports, DSMB reports related to the onsite event.
- Any changes to the protocol or IB resulting from the AE or UP report.
- For on-site AE's or UP's, a detailed description of the AE, UP, experience, or outcome including the severity of the event per NCI "Common Terminology Criteria for Adverse Events v3.0", and whether or not the event has resolved (FDA Med Watch report may be used when appropriate), all relevant electronic medical record entries, reports of contact, discharge summaries, or other documents as appropriate, an explanation of the basis for determining that the AE/UP represents an unanticipated problem, and a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the AE/UP.

Upon receipt of an AE/UP Reporting Form and ancillary documents from a Principal Investigator, the Research Office staff stamps the AE/UP report form with a date of receipt and check the form for completeness.

If any applicable sections of the Adverse Event (AE) Reporting Form are incomplete or have been answered unsatisfactorily, the IRB staff will return the form and any attachments to the Principal Investigator with a written explanation and a deadline for response. A copy of the form is kept with the IRB records until the original is returned.

At the discretion of the IRB staff, the Principal Investigator or the designated contact person may be contacted to make the corrections in the Research Office instead of returning the Adverse Event (AE) Reporting Form to the Principal Investigator.

The IRB Staff will track the Adverse Event (AE) Reporting Forms returned to the Principal Investigator and their response.

* The IRB considers failure to follow this policy to be non-compliance

Documentation of Whether or Not Action is Warranted

After taking into account considerations including, but not limited to, whether or not the study still meets IRB approval criteria under 38 CFR 16.111 and 38 CFR 16.116 (such as whether or not the risks to subjects have changed; whether or not the risk to benefit ratio has changed; and whether or not this constitutes new information that needs to be given to the subjects), the qualified IRB voting member-reviewer (or the convened IRB) must document whether or not one of the following applies in accordance with VHA Handbook 1058.01:

- Immediate Action Warranted. Immediate action (e.g., suspension of activities; notification of subjects) is necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii), and review by the convened IRB is needed; or
- No Immediate Action Warranted. Review by the convened IRB is needed, but immediate action to prevent an immediate hazard to subjects is not warranted.

Reporting to Convened IRB. If the preceding determinations are made by a qualified IRB voting member reviewer, the determinations must be reported to the IRB at the IRB's next convened meeting in accordance with VHA Handbook 1058.01.

Reporting to the Facility Director. If the qualified IRB voting member reviewer (or the convened IRB) determines that the AE is serious, unanticipated, and related, or probably related, to the research, the IRB Chairperson must report the event to the VA facility Director as soon as possible, but no later than 5 business days after the determination (VHA Handbook 1058.01). The VA facility Director then has an additional 5 business days to report the following events to ORO (VHA Handbook 1058.01):

- *Problems involving risks to subjects or others that are unanticipated and serious and related to the research (e.g., work-related injuries requiring more than minor medical intervention or extended surveillance or leading to serious complications or death; interruptions related to safety, rights, or welfare of subjects or others; VA National Pharmacy Benefits Management (PBM), Data Monitoring Committee (DMC) or sponsor safety reports).*
- *Local Serious AEs (SAEs) that are unanticipated and related to the research.*
- *Research Compliance Officer (RCO) audit findings of apparent serious or continuing noncompliance (also report to VISN and ORD).*
- *Institutional Review Board (IRB) findings of serious or continuing noncompliance (also report to VISN and ORD).*
- *Suspensions or terminations of study activities related to safety, rights, or welfare of subjects or others.*

Informed Consent Modifications. If it is determined that an informed consent

modification is warranted, the convened IRB must determine and document in its records whether or not 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 VHA Handbook 1058.01).

If the IRB Chair or designee or the full IRB request any modification to the consent document or research protocol, or addendum consent, the IRB Chair or designee will communicate to the Principal Investigator the requirement to submit the modifications to the IRB for review. If the IRB does not receive the complete modification or a satisfactory explanation as to why the modification could not be completed within four weeks.

- The PI is sent a Notification indicating failure to comply with a request for modification.
- The research may be suspended following IRB SOP "Suspension and Termination of Approved Research by the IRB."
- The PI may become ineligible to submit new research.

***Adverse Events of Research-Related Clinical Care.** When subjects experience adverse events while undergoing clinical care that is part of a research study, the clinical care adverse events must be disclosed to subjects in accordance with current VHA policy.

ACTIONS TAKEN AFTER IRB REVIEW

Following review of AE/UP's, the convened IRB may recommend the following:

- No further action required.
- Modification of the consent document.
- Providing additional information to current and/or prior research participants.
- Require re-consent of current research participants following the provision of additional information (via revised ICF or informational document) that may relate to the participant's willingness to continue to take part in the research.
- A modification in the continuing review interval.
- Additional monitoring of the research.
- Monitoring the consent process.
- Referral to other organizational entities such as the R&D committee.
- Suspension or termination of the research

Procedures for Reporting to External Agencies

For events that require reporting outside of the facility, Research Compliance Officer or designee will prepare the notification letter to be reviewed and signed by the Institutional Official. Reports are to be sent within 5 working days of the IRB's determination.

- All unexpected deaths of a research subject as determined by the IRB, and all events resulting in a "substantive IRB action" require reporting to ORO.

- All unanticipated problems involving risks to research participants or others must be reported to ORO and OHRP.
- FDA is to also be notified when the research comes under regulatory authority of the FDA.
- VA Privacy Office must be notified when the event involves unauthorized use, loss, or disclosure of individually identifiable protected patient information.
- VHA Information Security Officer must be notified when the event involves violations of VA information security requirements.

Reports should contain at minimum the following information.

- Name of the Institution conducting the research
- FWA number
- Complete protocol title including any applicable protocol numbers assigned either locally or by the sponsor or granting agency.
- Name of the principal investigator.
- A detailed description of the problem.
- Actions the institution is taking to address the problem (e.g. revise the protocol, suspend subject enrollment, terminate the research, revise the ICF, inform enrolled subjects, increase monitoring of subjects, etc.)

*An unexpected death of a research subject (see definition in HRPP SOP), as determined by the IRB, should be reported by the institutional official or designee to ORO no later than 24 hours after the IRB is informed of the death.

- If the IRB is unable to determine whether a research subject's death was unexpected after 5 working days of being informed of the death, the death must then be reported to ORO.
- When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to ORO.

If a federal agency funded the research, the IRB staff forwards a copy of the notification to the applicable federal agency.

If a sponsor other than a federal agency funded the research, the IRB staff forwards a copy of the notification to the sponsor.

*If an ON-SITE AE has occurred for a drug or device study that is closed locally, and the drug or device is currently approved for use by the FDA,

- the investigator should file a Med Watch 3500 form with the FDA and the sponsor, and include the name of the protocol in which the subject was participating.
- the information should be submitted to the IRB for review and approval, and does not require reopening the study unless otherwise indicated by the IRB.

Reporting Required of the PI for Off-Site Adverse Events/IND Safety Reports Provided by the Sponsor:

- All off-site adverse events are to be submitted to the IRB within 5 days of receipt.
- All DSMB minutes and quarterly AE reports will be reviewed by the full IRB as a notification.
- At the discretion of the Chairperson, any event may be referred for full-board for review.
- All off-site AEs/IND Safety Reports will be logged into the R&D office file and a letter of acknowledgement will be sent to the PI from the IRB Chair indicating receipt.

Record Keeping Procedures for Adverse Events and Unexpected Problems

- Adverse Event (AE) Reporting Form copies and any attachments are filed in the Research Office.
- Informed consent copies attached to the AE Reporting Form are destroyed once the form is reviewed and signed by the designated reviewer.
- The original signed AE reports are returned to the Principal Investigator after review by the full IRB.
- Reports for AE's or unanticipated problems in research or the imminent threat thereof are reported to the R&D via IRB minutes from meetings in which the AE or unanticipated problem in research and subsequent actions were discussed, ratified, or summarized.

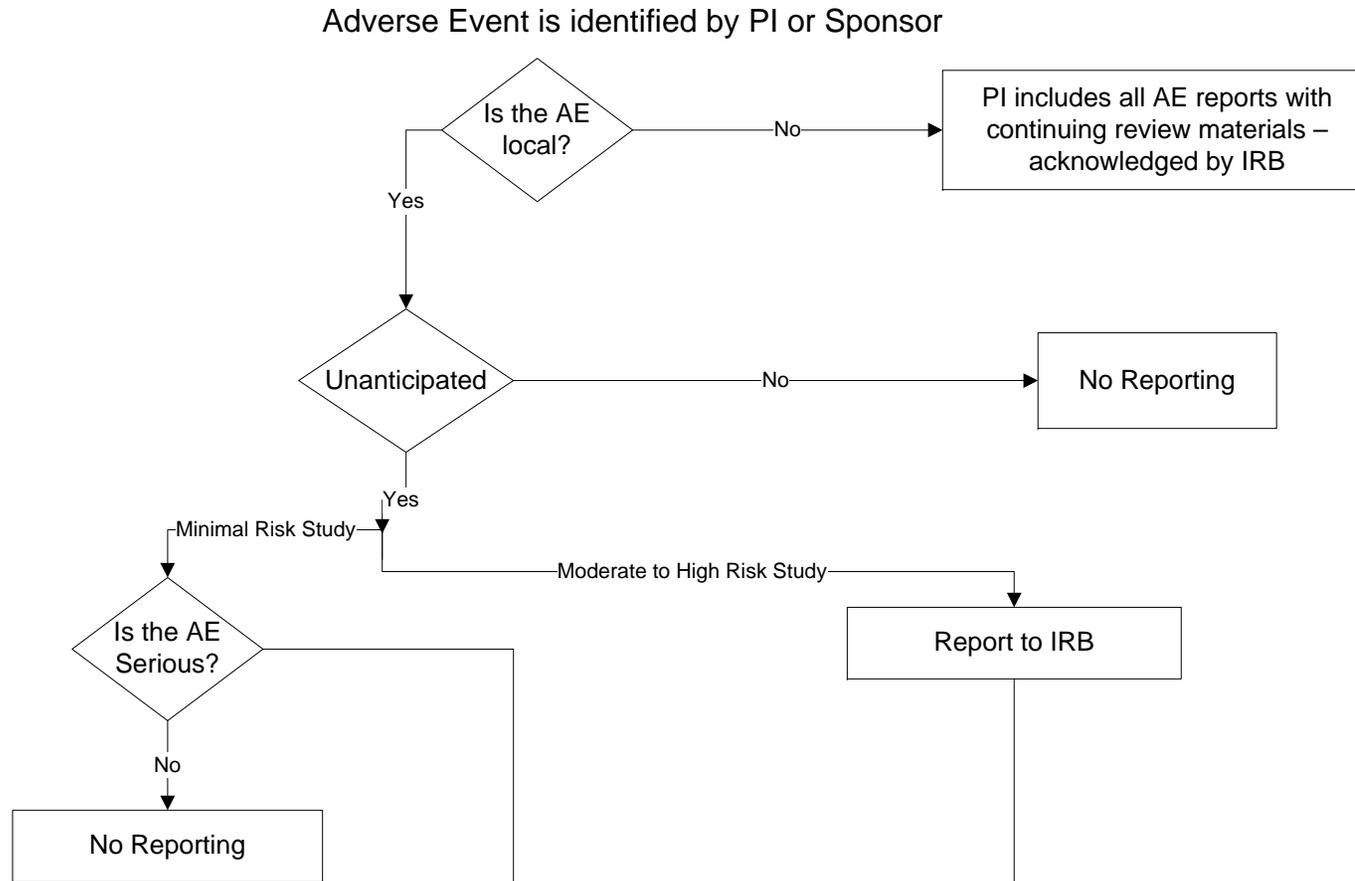
REFERENCE DOCUMENTS

- 45 CFR 46
- Guidance to Reporting Incidents to OHRP, May 27, 2005 21 CFR 312
- 38 CFR 16
- VHA Handbook 1058.01 Requirements for Reporting Events in Research to Facility Oversight Committees and the Office of Research Oversight
- VHA Handbook 1200.05 Requirements for the Protection of Human Subjects in Research
- VHA Memorandum from CRADO "Reporting Unanticipated Problems and Adverse Events to Institutional Review Boards", December 6, 2006.

* Note: Department of Defense components may have stricter requirements than the Common Rule requirements for reporting research-related injury.

Adverse Event Reporting Decision Tree

PI Decision Process



IRB Decision Process

