

**Department of Veterans Affairs
Tuscaloosa VA Medical Center**

Human Research Protection Program SOP #11

October 17, 2007

REPORTING REQUIREMENTS

1. POLICY

The Tuscaloosa VA Medical Center (TVAMC) Human Research Protection Program (HRPP) is committed to the protection of research participants while affording them the opportunity to participate in research.

It is the policy of the TVAMC to ensure the protection of research participants by compliance of written policies and procedures that define Institutional Review Board (IRB) reporting requirements. This standard operating procedure (SOP) establishes procedures for reporting and review of protocol deviations, adverse events (expected, unexpected, serious), unanticipated problems, and other required reports.

2. RESPONSIBILITIES

The TVAMC Medical Center Director has ultimate responsibility for ensuring the protection of human subjects by authorizing the IRB to monitor protocol deviations, adverse events, unanticipated events, and other required reports listed in this HRPP SOP.

TVAMC Institutional Review Board (IRB) is responsible for reviewing all protocol deviations, adverse events (expected, unexpected, serious), unanticipated problems, and other safety reports. In addition, the TVAMC IRB (through the R&D Committee) will comply with the VA memo dated 11/12/2003 regarding “What to report to ORO” (Appendix E).

Principal Investigators are responsible for his/her research project and for assessing and reporting protocol deviations, adverse events, unanticipated problems, and other safety reports occurring during a research study, as directed by this HRPP SOP.

3. DEFINITIONS

- a. Adverse event (AE):** An AE is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research, or any risk associated with the research or the research intervention, or the assessment.

- b. Serious Adverse Event (SAE):** A SAE is defined as death; a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.
- c. Unexpected Adverse Event (UAE):** An UAE is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.
- d. Expected Adverse Event (EAE):** An EAE is any adverse event that is already known (i.e. symptom of a premordid medical illness or known side effect of a medication listed in the informed consent and/or investigator brochure or product labeling).
- e. Adverse Drug Event (ADE):** An ADE is any adverse event and/or reaction that involves a drug which requires an intervention (discontinue current drug, lower dosage of current drug, add additional drugs, etc.).
- f. Imminent Threat of an AE in Research:** Any situation in which an AE in research has not yet occurred but is likely to occur, as determined by an IRB, research, or clinical team member, without preventative measures.
- g. Substantive Action:** An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.
- h. Unanticipated Problem involving risk to patient or others:** Any unanticipated serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a research procedure or drug, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application or investigator brochure or product labeling (see Unanticipated Problem Reporting Form for list).
- i. Unexpected Death:** The death of a research subject 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 clearly hastened the subject's death. A subject'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 to VA ORO Regional Office.

- j. Protocol Deviation (PD):** A PD (also called protocol violation) is defined as any intentional or non-intentional action taken by the investigator, research assistant, or research subject that deviates from the approved protocol, including errors and accidents. A PD is also defined as an unanticipated or unintentional divergence or departure from the expected conduct of an approved study that is not consistent with the current research protocol, consent documentation or study addenda. A PD typically does NOT have a significant effect on the subject's rights, safety, or welfare, or on the integrity of the resultant data. A PD may also involve prospective approval by the research sponsor for the local Investigator to accrue a subject who does not satisfy the approved inclusion/exclusion criteria for enrollment, although does not significantly affect the integrity of the resultant data. *NOTE: This definition may not match a sponsor's definition.*

Minor deviations by the subject such as missed doses or missed appointments do not constitute a protocol deviation. However, if the patient "non-compliance" is chronic such that investigator action that is not otherwise specified in the protocol is required, then a PD must be filed with the IRB.

Examples of a PD may include, but are not limited to:

- Changes in procedures initiated to eliminate immediate hazards to study subjects
- Signification variations/errors in drug dosing or timing of visits
- Use of prohibited medications
- Enrolling subjects who do not fulfill inclusion/exclusion criteria
- Protocol deviations/violations identified by sponsor monitor visits or study coordinator that may or may not affect the safety of a participant or the integrity of study data
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention which

Non-serious (minor) PD:

- Have no substantive effect on the safety or well-being of research participants
- Do not affect the value of the data collected (meaning the violation does not confound the scientific analysis of the results)
- Do not result from willful or knowing misconduct on the part of the investigator(s)
- Do not violate any ethical principles

Serious (major) PD:

- Have or pose a significant risk of substantive harm to research participants
- Cause damage to the scientific integrity of the data collected
- Result from evidence of willful or knowing misconduct on the part of the investigator
- Impact ethical principles

4. PROCEDURES

- a. Initial Research Plan:** At the time of initial review, the investigator must develop a research plan that is scientifically valid, minimizes risk to the subjects, and contains a

description of the data and safety monitoring plan The plan may vary depending on the potential risks, complexity, and nature of the study. A Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) may be indicated as part of the monitoring plan and may be required by NIH-funded studies or the FDA. See HRPP SOP#3 for details on requirements at initial review.

b. **Three-Tiered Reporting Mechanism:** The TVAMC HRPP has a three-tiered reporting mechanism, as outlined below:

1. **Prompt Reporting to the IRB (within 5 days).**
2. **Reports to IRB at the Time of Continuing Review or Study closure.**
3. **Reports to the IRB that Require Subsequent Reporting to VA of Office of Research Oversight.**

Other reporting may be required to other entities, such as the Food and Drug Administration (FDA), VA Office of Research and Development (ORD), Network Director, or other.

c. **Prompt Reporting to the IRB.** Problems listed in the Unanticipated Problem Reporting Form (see Addendum) include a listing of reportable unanticipated problems or events that involve risks to participant or others. The unanticipated problem is promptly reported (within 5 days of learning of the event) to the IRB Chair (and also reported in summary spreadsheet at the time of continuing review or study closure). The IRB Chair or designee will review the form within 5 working days and determine whether or not the event represents an unanticipated problem involving risks to subjects or others, which is defined as 1) information in the report is not expected given the nature of the research procedures and the subject population being studied and 2) the information in the report suggests that the research places the subjects or others at greater risk of harm or discomfort related to the research than was previously known or recognized. If the event is not considered an unanticipated problem, no further action is required by the IRB and the PI is instructed to include the problem in the spreadsheet or table format for submission at the time of continuing review and/or study closure.

If the event represents an unanticipated problem involving risks to subjects or others, the Chair or designee may take immediate action to suspend the research study if warranted by to safety concerns and the problem is referred to the convened IRB and possibly regulatory agencies and institutional officials (see below). The IRB or person ordering the suspension or termination will consider actions needed to protect the rights and welfare of currently enrolled participants, including informing current participants of the termination or suspension and having any adverse events or outcomes caused by the termination or suspension reported to the IRB. The PI is notified in writing of the decisions made by the IRB Chair and/or IRB. The IRB may request additional information from the investigator if needed. During review if the IRB Chair or his/her designee require additional information he/she may review the permanent study file and/or he/she may request the PI or sponsor to submit additional information for further review. He/she will determine if a consent form revision is required and to what extent

re-consenting and/or subject notification about new information is required. The IRB has the authority to suspend a study if it has significant concerns about safety. A letter is sent to the PI informing him/her of further action required. The action of the review depends upon factors such as the seriousness of the event, the health of the subject population, whether the event is felt to be study related, whether the event occurred with a TVAMC subject, the number of occurrences in relation to the size of the study, and whether the event is anticipated and already adequately described in the Informed Consent Form or other study documents.

If a study is suspended or terminated or if the unanticipated event represents an unanticipated problem involving risks to subjects or others (defined above), the Unanticipated Problem Reporting Form or other appropriate report or notice is also reported within a timely manner to the following:

- IRB
- The R&D Committee, which gets submitted through the minutes to the TVAMC Director through the Chief of Staff.
- OHRP, if the study is subject to DHHS regulations or subject to a DHHS federal-wide assurance
- The FDA, if the study is subject to FDA regulations
- The VA Regional ORO, if it meets the definition listed below
- The VA Office of Research and Development, if the research is VA-funded
- Any “Common Rule” Federal Agency that is supporting the research
- The Sponsor, if the study is sponsored
- The Privacy Officer, if the report involves unauthorized use, loss, or disclosure of individually identifiable patient information
- The information Security Officer, if the report involves violations of information security requirements
- Others as deemed appropriate by the TVAMC Director
- Current study participants, when the study is terminated or suspended or when such information might relate to participants’ willingness to continue to take part in the research

As a means to ensure prompt reporting to the IRB, appropriate institutional officials, and the FDA of Unanticipated Problems, the IRB approval letter "Conditions of IRB Approval" informs investigators that all Unanticipated Problems involving risk to subjects or others must be promptly reported to the IRB and the sponsor.

In addition, any reports from a Data Safety Monitoring Board, must be promptly reported to the IRB Chair for review and forwarding to the full IRB review at a convened meeting.

- d. **Reports to the IRB at the Time of Continuing Review or Study Closure.** All adverse events (expected or unexpected), serious adverse events, protocol deviations, safety reports, and other items that are not listed on the Unanticipated Problem Reporting Form are to be recorded by the investigator in their study documents at the time of the event

and summarized in a spreadsheet/table format to be turned in at the time of continuing review or study closure. In addition, all SAEs involving must follow the reporting requirements of any DSMB, sponsor or if applicable, the FDA. Adverse drug events are required to be reported to the Pharmacy service, promptly, using the Pharmacy adverse drug form.

- e. Reports to the IRB that Require Subsequent Reporting to VA of Office of Research Oversight:** The TVAMC will comply with the instructions of ORO memo dated September 8, 2005 “What to Report to ORO.” The following criteria for AEs must be reported in the time-frame indicated. All AEs in research and imminent threats of AEs in research conducted on site that result in either:

(1) An IRB taking substantive action(s) as defined above. A written report of the AE in research (or an imminent threat thereof), VA form 10-0420, and the IRB action(s) to be taken, must be submitted to the ORO Regional Office within 10 working days of the IRB’s determination to take such action(s).

Or

(2) An unexpected death of a research subject, regardless of IRB action. Such deaths must be reported to the ORO RO within 24 hours after the IRB determines that the death was unexpected, as defined above. If the IRB is unable to determine whether a research subject’s death was unexpected after 10 working days of being informed of the death, the death must then be reported to the ORO RO. When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to ORO.

The institutional official (VHA facility Director), or designee, must:

(1) Prepare a separate report, for each AE in research (or imminent threat thereof), meeting the above criteria, following the format in Appendix A of VA Handbook 1058.1.

(2) Initial the completed report and facilitate its submission to the Director of ORO RO that oversees the VHA facility, using express mail (e.g., Fed Ex) and either e-mail or fax. A copy of all IRB minutes from meetings in which the AE in research and subsequent actions were discussed, ratified, or summarized needs to accompany the report to the ORO RO, or be sent when the IRB minutes become available, but no later than 4 wks after the IRB meeting.

f.

5. REFERENCES

- VA Directive 1200.5
- VHA Handbook 1058.1
- 38 CFR 16.102
- 21 CFR Parts 50, 54, 56, 312, 314, 812, and 814

6. ATTACHMENTS

- Adverse Event Form
- Serious Adverse Event Form
- Protocol Deviation Form

7. **RESCISSIONS**

TVAMC HRPP SOP#11 May 7, 2007.
Adverse Event Form
Serious Adverse Event Form
Protocol Deviation Form

8. **REVIEW DATE**

January 1, 2012

Signature on File in R&D Office
Lori L. Davis, MD
Coordinator of Research and Development