Human Research Protection Program SOP #11 Revised March 31, 2016

REPORTING REQUIREMENTS

1. POLICY

The Birmingham VA Medical Center (BVAMC) 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 BVAMC 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 including deaths), unanticipated problems, and other required reports.

2. RESPONSIBILITIES

The BVAMC Medical Center Director (MCD) 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. The MCD must ensure that ORO is notified within 2 business days of any research-related citation or determination of regulatory noncompliance issued by any State or Federal agency; or any situation covered by VHA Handbook 1058.01 that has generated media attention or Congressional interest.

BVAMC Institutional Review Board (IRB) is responsible for reviewing all protocol deviations, adverse events (expected, unexpected, serious), unanticipated problems, and other safety reports. Additionally, the BVAMC IRB (through the R&D Committee) will comply with the VHA Handbook 1058.01 Research Compliance Reporting Requirements.

Principal Investigators (PI) are responsible for his/her research project and for assessing and reporting (using IRB SAE/AE/UAP reporting form) protocol deviations, adverse events, unanticipated problems, and other safety reports occurring during a research study, as directed by this HRPP SOP to the IRB. If the event involves investigational drugs (listed on the VA 10-9012 form) copies of the report, SAE/AE/UAP or other forms must be sent to Pharmacy as well as the IRB.

Research Compliance Officer (RCO) is responsible for notifying the Office of Research Oversight (ORO) of IRB determinations of SAEs meeting the reportable requirements of ORO and deaths related to research.
3. **DEFINITIONS**

See HRPP SOP#24 – HRPP Definitions

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. **Investigator Prompt Reporting to the IRB.** SAE/AE/UAP Reporting Form or the Deviations/Violations Reporting form should state what the problem is (a complete description) and include the reportable unanticipated problem or event involved. VA Personnel, including WOC and IPA appointees, must ensure oral notification to the IRB immediately upon becoming aware of any local research death that is both unanticipated and related to the research. Written notification of a local research death, local SAE or serious problem to the IRB is required within 5 business days after becoming aware of the incidents that are both unanticipated and related to the research. If the event occurred with a Department of Defense (DOD) funded study this event must be reported to the DOD and the IRB.

   The IRB Letter of Assurance informs investigators that all Unanticipated Problems involving risk to participants or others must be promptly reported to the IRB, Research Pharmacist (if drugs are involved), the sponsor (if applicable), and the FDA (if applicable).

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

   Principal Investigators must report any unanticipated problem to the IRB (and Pharmacy if drugs are involved) and these unanticipated problems may include:

   1) Unanticipated adverse event (AE): any harm experienced by a participant, which in the opinion of the principal investigator is both unexpected and related.

      a) An adverse event is “unexpected” when its specificity and severity are not accurately reflected in the informed consent document.

      b) An adverse event is “related to the research procedures” if in the opinion of the principal investigator, it was more likely than not to be caused by the research
procedures or if it is more likely than not that the event affects the rights and welfare of current participants.

2) Information that indicates a change to the risks or potential benefits of the research. For example:
   a) An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
   b) A paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.

3) A breach of confidentiality.

4) Internal adverse events, which are unexpected and related to the research

5) External adverse events which are unanticipated problems involving risks to subjects or others

6) Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm

7) Change in FDA labeling or withdrawal from marketing of a drug or biologic used in a research protocol.

8) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.

9) Incarceration of a participant in a protocol not approved for enrolled prisoners.

10) Event that requires prompt reporting to the sponsor.

11) Sponsor imposed suspension for risk.

12) Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.

13) Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm. This would include enrolled subjects, thus putting them at risk when they do not meet entry criteria.

14) Unanticipated serious event is defined as any serious adverse event that affects the health or safety or any life-threatening problem or death caused by, or associated with, a study related procedures or study drug, 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 study procedure or study medication that relates to the rights, safety, or welfare of subjects at the local level. Events that occur at other sites (such as with CSP studies and multi-site) must be reported but may be reported at continuing review on a spreadsheet unless the event is an unanticipated problem that affects the safety of participants on a local level.
15) Other unanticipated information that indicates subjects or others might be at increased risk of harm.

The IRB will accept other reports when the investigator is unsure whether the event should be reported.

c. **IRB Review**: Within 5 business days after a report of a serious unanticipated problem involving risks to subjects or others, the convened IRB or a qualified IRB member-reviewer must determine and document whether or not the reported incident was serious, unanticipated, and related to the research.

The action of the review depends upon many factors, such as:

- the level of risk or 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 BVAMC participant,
- 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.

IRB members are provided with copies of the SAE/AE/UAP form, Protocol and or Informed consent involved with the unanticipated event for determination of further action. In addition, members may request the investigator’s brochure (on file in the IRB office), if one exists or is available. The members may wish to access the entire IRB file for a more detailed review, or may request additional information from the investigator, if needed.

d. **IRB Determination/Action**

1) If the event is considered to be an anticipated problem OR 2) the participants or others are NOT at increased risk of harm), the IRB Chair or designee indicates this determination on the SAE/AE/UAP form or Protocol Violation/Deviation form.

   a) A copy of the signed form is returned to the investigator and serves as written communication.

   b) If the IRB and/or the investigator indicated that the consent document, or protocol should be revised, the 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. The investigator must follow the procedures outlined in IRB SOP#20 IRB Modification Review for submitting a protocol and/or informed consent document amendment.

   c) If modifications are not necessary then no further action is required by the IRB and the PI is instructed to include the event (SAE and/or Deviation) into a spreadsheet or table format for submission at the time of continuing review and/or study closure per IRB instructions included with continuing review materials.
2) 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 report the problem or event directly (without intermediaries) to the facility Director within 5 business days after the determination.

3) The convened IRB will consider and may request one or more of the following actions as it pertains to items 1) or 2) above:
   1. Suspension of the study
   2. Modification of the protocol and/or consent form
   3. Modification of the information disclosed during the consent process
   4. Provision of additional information to current participants (mandatory whenever information may relate to participant's willingness to continue participation)
   5. Provision of additional information to past participants
   6. Requirement for current participants to re-consent to participation
   7. Alteration of the frequency of continuing review
   8. Observation of the research or the consent process
   9. Subject notification about new information
   10. Requirement for additional training of the investigator or other research staff
   11. Notification of investigators at other sites
   12. Termination or suspension of the research
   13. Provision of additional information to the IRB
   14. Determination that no action is required

4) **Suspension**: The IRB, the Chair, or Designee ordering the suspension or termination will, in consultation with the Chief of Staff, consider actions needed to protect the rights and welfare of currently enrolled participants (i.e. to stop or continue their participation), 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.

e. **IRB Notification to Investigator**: The PI is notified in writing of the decisions and if applicable, the recommendations or actions required by the IRB. The PI must promptly attend to these actions or recommendations.

f. **Reports to the IRB at the Time of Continuing Review or Study Closure**: All local adverse events (expected, unexpected, related or not-related), serious adverse events, protocol deviations and safety reports, 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. Events that occur at other sites (as in CSP or studies with multi-sites) must be reported at continuing review to the local IRB. In addition, all SAEs must follow the reporting requirements of any DSMB,
sponsor or if applicable, the FDA. Adverse drug events are required to be reported promptly to the Research Pharmacist.

g. **Reports to the IRB that Require Subsequent Reporting to VA Office of Southern Regional Office (SRO) and/or (Office of Research Oversight (ORO).** The BVAMC will comply with the instructions from ORO in Handbook 1058.01 Research Compliance Reporting Requirements. The following criteria for AEs must be reported in the timeframe indicated. All AEs in research conducted on site that result in:

1) The convened IRB or the qualified IRB member-reviewer determining that the problem or event is serious **and** unanticipated **and** related to the research must report the problem or event **directly** (without intermediaries) to the facility Director within 5 business days after the determination.

   a) The IRB action(s) to be taken will be submitted to the Medical Center Director (MCD) by the RCO. The MCD will report this to SRO within 5 business days of after the notification.

   b) The RCO has been designated to notify SRO/ORO and the Medical Center Director.

2) The IRB will alert ORO by email or telephone within 2 business days after receiving immediate oral notification from the Investigator of a local research death that is believed to be both unanticipated and related to the research.

3) The IRB Chair or a qualified IRB member review is required to determine/document whether actions are warranted to eliminate apparent immediated hazards to subjects within 5 business days after receiving written notification of the death. The IRB must determine and document at the next convened meeting that the death was or was not unanticipated and related to the research or there is insufficient information to make a determination. They must determine and document whether modifications are warranted; and whether/when/how investigators must notify or solicit renewed consent from enrolled subjects. They must notify the Medical Center Director and the ACOS/R&D within 5 business days of determinations. The facility director must report to ORO within 5 business days after notification.

   a) The RCO has been designated to notify SRO/ORO and the Medical Center Director.

**Report of any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility’s research projects will be forwarded directly to the Chief of Staff.**

1) The Chief of Staff is required to forward these communications to the ACOS for
Research.

2) The ACOS for Research, in turn, will determine if any of the facility’s research projects are affected and will forward any communication affecting an active research project to the IRB and the relevant investigators.

3) The IRB must address such alerts at scheduled IRB meetings.

h. The Research Compliance Officer will:
   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 1058.01 Research Compliance Reporting Requirements.

2) Submit the report to the BVAMC Director, the Associate Chief of Staff, Research and Development, and the Research and Development Committee Chair for acknowledgement and signature.

3) The completed, signed report is submitted to the Director of SRO/ORO and OHRP using express mail (e.g., Fed Ex) or scanned by e-mail using PKI. 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 ORO and OHRP, or be sent when the IRB minutes become available, but no later than 4 weeks after the IRB meeting.

i. The following research events must be reported to SRO:
   1) Local Serious AEs (SAEs) that are unanticipated and serious and related to the research.
   2) Research Compliance Officer (RCO) audit findings of apparent serious or continuing noncompliance.
      o Must also be reported to ORD
   3) Institutional Review Board (IRB) findings of serious or continuing noncompliance.
      o Must also be reported to ORD
   4) Suspensions or terminations of study activities related to safety, rights, or welfare of subjects or others.
   5) Any proposed change in facility’s Federalwide Assurance (FWA) or other ORO-approved Assurance.

j. Changes in the facility’s Human Research Protection Program requiring notification to ORO and RCEP with a copy to SRO:
   1) Assurance changes
   2) IRB designation changes
   3) IRB roster changes
   4) Substantive MOU changes
   5) RCO changes
   6) Accreditation status change
k. Report to ACOS for Research, Privacy Officer (PO), and Information Security Officer (ISO) immediately of any suspected or confirmed unauthorized use, disclosure, transmission, removal, theft, loss, or destruction of VA research-related protected health information (PHI), individually identifiable privacy information, or confidential information, as defined by the HIPAA Privacy Rule, the Common Rule, the Privacy Act, or 38 U.S.C. 5701, 5705 and 7332. The ACOS will forward this report to the Medical Center Director within 1 hour of receipt.

1. Report to ACOS for Research, PO and ISO within 5 business days is required for:
   1) Findings of non-compliance related research information security or privacy by entities external to the facility
   2) Any other deficiency that substantively compromises the effectiveness of the facility’s research information protection program.
   3) Suspensions or terminations of research related to information protection concerns.
   4)

5. REFERENCES
   - VHA Handbook 1200.05 Requirements for the Protection of Human Subjects in Research
   - VHA Handbook 1058.01, Research Compliance Reporting Requirements
   - Title 38 CFR 16.102
   - Title 21 CFR Parts 50, 54, 56, 312, 314, 812, and 814

6. ATTACHMENTS
   SAE/AE Reporting Form
   Protocol Deviations/Violations Reporting Form
   Protocol Amendment form
   Miscellaneous Form
   ORO Notification Request
   SRO/ORO Notification Request
   RCO Reporting of Apparent Serious or Continuing Noncompliance

7. REVISIONS

8. REVIEW DATE
   February 2021

[Signature]
Louis Dell'Italia, MD
ACOS, Research and Development