

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

SOP# HRP 01.08

Version	1.1	Origin	Version 1.0
Author	Jessica Mendoza		
Reviewed/ Revised by	Jessica Mendoza	Dates Reviewed / Revised	4/27/11
Changes	Revisions for AAHRPP Step 1 review	New Version #	1.1
Approved	Christopher T. Bever, ACOS/R&D Date		
File Name	\\Reportable Events (HRP 01.08) 2011v1.1		

REPORTABLE EVENTS

OBJECTIVE:

- To establish a documented process for reporting and responding to serious unanticipated problems, unanticipated serious adverse events, and apparent serious or continuing noncompliance.
- To assure the safety of human research participants through the development of action plans by principal investigators to prevent recurrence and to promote future compliance
- To educate research staff to assure they understand applicable regulations, guidelines, policies and procedures

SCOPE & POLICY:

In May 2010, the VHA Office of Research Oversight (ORO) issued VHA Handbook 1058.01, "Research Compliance Reporting Requirements" that set forth the requirements for reporting certain research events to facility officials, relevant research review committees, and the ORO. The handbook identifies research events that must be reported to facility entities, ORO Regional Offices, and ORO Central Office and the methods, timelines and specifics for the reports. The Handbook also delineates the reporting requirements for apparent serious or continuing noncompliance found through Research Compliance Officer (RCO) audits vs. reporting requirements for other types of events or possible noncompliance. This SOP covers the human research portions of Handbook 1058.01 with emphasis on the role of the VAMHCS R&D Service and its investigators.

In October 2008, the VHA Office of Research Oversight (ORO) formally established the role of Research Compliance Officer (RCO) and a mandatory research compliance audit program of signed informed consent forms and triennial regulatory audits of research studies.

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

The University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) and the VA Central IRB (CIRB) are the IRBs of record for VAMHCS research projects and as such, they must determine whether “apparent serious or continuing noncompliance” reported by the RCO is serious or continuing noncompliance. The IRB must also approve the corrective action plan for resolving the noncompliance. The R&D Committee (RDC) may add further actions with notification to the IRB, but may not delete any actions required by the IRB.

The VAMHCS takes seriously any issue of noncompliance of research staff with regard to human subject protections and research integrity. Because the Research Service is responsible for the conduct of research by VA investigators, it has a role in ensuring that corrective actions are resolved and may need to engage actively with investigators to achieve this goal. Therefore the VAMHCS Research Service will support:

- the independence and actions of the RCO,
- the corrective actions required by the RCO and/or the IRB and RDC,
- the MCD role in assignment of additional audits.

RESPONSIBILITIES:

Compliance with institutional and regulatory policies and procedures is an ongoing responsibility of everyone involved in the VAMHCS research program.

The ACOS/R&D is responsible for:

- Determining if any of the facility’s research projects are affected by PBM alerts and, if so, reporting the alert to the IRB and the relevant investigators.
- working collaboratively with the RCO to promote research compliance among researchers;
- ensuring that corrective action plans are implemented and resolved;
- Allowing the RCO to work independently of the R&D Service;
- Notifying the MCD of noncompliance not found through RCO audits as described in VHA HB 1058.01.

The Research Compliance Officer (RCO) is responsible for:

- Conducting the ORO mandatory audit program as described in VHA Handbook 1058.01;
- Informing principal investigators of ORC audit results promptly and accurately;
- Notifying appropriate individuals and committees of “apparent serious or continuing noncompliance” according to VHA Handbook 1058.01;
- Informing the IRB, RDC and other relevant research review committees of the results of all RCO informed consent audits and regulatory audits, regardless of outcome, in a timely fashion.
- Assisting the MCD with initial reports and follow-up reports to ORO as described in HB 1058.01
- Assisting the IRB, as requested, with information necessary for deliberations on cases of “apparent serious or continuing noncompliance” and its determinations of serious or continuing noncompliance;

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

- Refraining from imposing remedial actions for identified noncompliance rather than recommending actions to the relevant research oversight committee;
- reporting apparent serious or continuing noncompliance to the MCD, the COS, the ACOS/R&D, R&D Committee Chair, IRB Chair, the HRPO Director of Compliance, other VAMHCS entities, regulatory agencies, and sponsors as delineated in this SOP
- serving as a consultant, as needed, to the facility's R&D Committee, IRB, and other committees as requested (the RCO may not be a voting or nonvoting member of these committees);
- Meeting regularly with the Medical Center Director (MCD) to update the MCD on progress and concerns related to the Office of Research Compliance;
- Regularly attending ORO monthly conference calls.

The R&D Committee is responsible for:

- reviewing the results of audits conducted by the RCO/ORC;
- reviewing IRB determinations of serious or continuing noncompliance;
- reviewing the corrective action plan as presented or requiring additional steps to remedy the noncompliance;
- deliberating research compliance issues that are not under the purview of the IRB or other subcommittees;
- other assistance as requested by the RCO.

The Principal Investigator is responsible for:

- being compliant with institutional and regulatory policies and procedures that protect the rights and safety of research participants and the scientific integrity of their research projects;
- ensuring that research team members are compliant with all local and VA requirements;
- reporting incidents of noncompliance or unanticipated problems to the IRB according to this SOP and IRB policies and procedures;
- cooperating with audits and investigations of complaints or allegations of noncompliance,
- notifying the the IRB when a complaint has occurred or potential noncompliance is discovered;
- responding to queries and corrective action plans (CAPs) in a timely manner,
- notifying study participants and sponsors as directed by the RCO/IRB.

DEFINITIONS:

Active study. An “active” study is a study approved by and under continuing oversight from the Research and Development Committee (R&DC), Institutional Review Board (IRB), Institutional Animal Care and Use Committee (IACUC), Subcommittee on Research Safety (SRS), or other VA or VA-designated research oversight committee, regardless of whether the study is “open” or “closed” to accrual.

Allegation of noncompliance: an assertion without proof or before proving that an act or practice of noncompliance has occurred or is occurring.

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

Completed study. A “completed” study is a study for which oversight by all relevant research oversight committees has been concluded.

Continuing noncompliance Continuing noncompliance is a persistent failure to adhere to the laws, regulations, or policies governing human research [VHA HB 1058.01 4.e].

Noncompliance is the failure to comply with applicable Federal Regulations, UMB IRB and Human Research Protections Program policies and procedures, UMB policy, or the requirements or determinations of the UMB IRB. For VA research this also includes non-compliance with the requirements of VA regulations or directives.

RCO audit. RCO audits are audits conducted, supervised, or verified by the facility’s lead RCO.

Serious AE (SAE). An SAE is an AE 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. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome.

Serious noncompliance is a failure to adhere to the laws, regulations, or policies governing human research that may reasonably be regarded as:

- (1) Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
- (2) Substantively compromising the effectiveness of a facility’s human research protection or human research oversight programs. [VHA HB 1058.01 4.x].

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

- (1) Involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or
- (2) Substantively compromising the effectiveness of a facility’s human research protection or human research oversight programs. [VHA HB 1058.01 4.y]

Unanticipated (Unexpected). The terms “unanticipated” and “unexpected” refer to an event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population

SEE ALSO

VHA Handbook 1058.01	Research Compliance Reporting Requirements
VHA Directive 2008-079	
VAMHCS Policy 512-00-010	Research Compliance
Research Service SOP	HRP 01.07: Comments, Complaints and Suggestions Related

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

	to the Human Research Protection Program
Research Service SOP	HRP 01.09: Conducting Human Participants Research at the VAMHCS: The Relationship of VAMHCS Research Standard Operating Procedures to the Policies and Procedures of the UMB Human Research Protections Office (HRPO)
UMB HRPP Policies & Procedures	Available online at http://www.hrpo.umaryland.edu/policies.asp

PROCEDURES:

1. Actions and Notifications for Determinations of Serious/Continuing Noncompliance
 - 1.1. Within 5 business days of becoming aware of any possible or “apparent serious or continuing noncompliance”¹, members of the research community are required to ensure that the apparent noncompliance has been reported in writing to the IRB through CICERO.
 - 1.2. Within 5 business days of identifying “apparent serious or continuing noncompliance”² based on an informed consent audit, regulatory audit, or other systematic audit of VA research, the RCO reports the apparent noncompliance directly (without intermediaries) to the MCD, COS, ACOS/R&D, RDC Chair(s), IRB Chair, UMB HRPO Director of Compliance, and other relevant research review committees or institutional officials such as the VAMHCS ISO (when the report involves violations of VA information security requirements) or PO (when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information).
 - 1.3. Within 5 business days of receiving the RCO notification, the MCD reports the apparent serious or continuing noncompliance in writing to ORO Southern regional office (SRO), VISN 5 Director, VISN 5 Medical Officer, and ORD.
 - 1.3.1. The notification must contain the elements required by ORO (see Attachment 1).
 - 1.3.2. The RCO ensures that the notification is sent to ORO via encrypted email.
 - 1.4. All actions above (1.2-1.3) are required regardless of whether disposition of the matter has been resolved at the time of the notification.
 - 1.5. The UMB HRPO/IRB processes the notification according to their policies and procedures, that are consistent with VHA handbook 1058.01. This includes:
 - 1.5.1. The IRB must review any report of apparent serious or continuing noncompliance at its next convened meeting.
 - 1.5.2. Should the IRB determine that the reported incident constitutes serious noncompliance or continuing noncompliance, the IRB Chair, or designee must report the determination directly (without intermediaries) in writing to the MCD with simultaneous copies to the ACOS/R&D, RDC Chair, and any other relevant research review committee within 5 business days after the determination.
 - 1.5.3. The MCD must report the determination to SRO, with a simultaneous copy to the VISN Director, VISN Medical Officer, and the ORD, within 5 business days after receiving such notification, unless the noncompliance has already been reported.

¹ See Attachment I

² See Attachment I

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

- 1.5.4. An initial report of an IRB determination that serious noncompliance or continuing noncompliance occurred is required, even where the determination is preliminary or disposition of the matter has not been resolved at the time of the report.
 - 1.5.5. The IRB must reach a determination that serious or continuing noncompliance did (or did not) occur within 30-45 days after receiving a report of apparent noncompliance.
 - 1.5.6. Remedial actions involving a specific study or research team must be completed within 90-120 days after the IRB's determination. Remedial actions involving programmatic noncompliance must be completed within 120-180 days after the IRB's determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, legal negotiations, etc.
 - 1.5.7. If the applicable deadlines cannot be accomplished, the RCO must report the reasons and progress to the MCD, R&D Committee and ORO (if applicable). The facility must provide ORO with a written justification for the delay and an acceptable timeline for completion
2. Actions and Notifications for Serious Unanticipated Problems Involving Risks to Subjects or Others (UPR) OR Local Unanticipated SAEs
- 2.1. Members of the VAMHCS research community must report UPRs according to IRB procedures.
 - 2.2. Members of the VAMHCS research community must report any serious UPRs to the IRB via CICERO within 5 business days of becoming aware of the problem. Serious UPRs include;
 - 2.2.1. Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others;
 - 2.2.2. Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death;
 - 2.2.3. 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.
 - 2.2.4. Any sponsor analysis describing a safety problem for which action at the facility level may be warranted.
 - 2.2.5. Any DMC, DSMB, or DSMC report describing a safety problem;
 - 2.2.6. 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;
 - 2.2.7. Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs
 - 2.3. Members of the VAMHCS research community must report any local (i.e., occurring in the reporting individual's own facility) unanticipated SAE in VA research, to the IRB via CICERO within 5 business days of becoming aware of the SAE.
 - 2.3.1. *The unfounded classification of an SAE as "anticipated" constitutes serious noncompliance.*

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

- 2.4. The UMB HRPO/IRB processes the notification according to their policies and procedures that are consistent with VHA handbook 1058.01.
- 2.4.1. 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 with a simultaneous copy to the ACOS for Research and the R&D Committee Chair.
- 2.4.2. A simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of subjects) necessary to prevent an immediate hazard to subjects in accordance with VA regulations at 38 CFR 16.103(b)(4)(iii).
- 2.4.3. All determinations of the qualified IRB member-reviewer (regardless of outcome) must be reported to the IRB at its next convened meeting. The convened IRB must determine and document whether or not a protocol or informed consent modification is warranted, 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.
- 2.5. The VAMHCS MCD reports the problem or event to the Southern Regional Office (SRO) of ORO within 5 business days after receiving a notification of a problem or event is serious and unanticipated and related to the research.

3. ORO Requirements for Reporting

- 3.1. Initial Notification of apparent serious or continuing noncompliance: see items 5.1-5.6.
- 3.2. Updates (Follow-up Report):
- 3.2.1. Updates to ORO regional office (Southern Regional Office; SRO) as requested or as additional information is available.
- 3.2.2. Updates must incorporate the full scope of relevant determinations and remedial actions, including programmatic actions as warranted. If a letter to OHRP has been sent by the UMB HRPO or the VAMHCS, updates may refer to those letter(s) (see item 6).
- 3.2.3. Updates may be sent directly from the RCO via email to ORO RO cc'd to VAMHCS leadership (the MCD, COS, ACOS/R&D, RDC Chair, relevant administrative staff) and VISN 05 (Network Director, Network medical officer, relevant administrative staff).
- 3.2.4. Formal letter(s) or cover letter(s) to ORO RO are reviewed and approved by the MCD and the COS before being signed by the MCD. Scanned copies of the signed documents are sent to ORO via encrypted email.
- 3.3. If the applicable deadlines for the CAP cannot be accomplished, the RCO must report the reasons and progress to the MCD, R&D Committee and ORO according to item 5.7.6. The facility must provide ORO with a written justification for the delay and an acceptable timeline for completion.

4. Reports to Other Entities

- 4.1. If the IRB determines that serious or continuing noncompliance or unanticipated serious problem has occurred, the MCD must notify OHRP.
- 4.1.1. The HRPO processes a letter of determination to be sent to the DHHS Office of Human Research Protections (OHRP) according to IRB P&P. This letter is sent to the VAMHCS MCD and other relevant officials.

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

- 4.1.2. The MCD forwards the letter to OHRP and ORO accompanied by explanatory cover letter to OHRP and ORO that is signed by the MCD.
- 4.1.3. Alternatively, the RCO may draft a letter to OHRP, send it to the HRPO Director of Compliance for review, and send it to OHRP through the MCD as in item 5.5 with distribution to the HRPO and VAMHCS officials.
- 4.1.4. The issue is placed on the agenda of the next scheduled R&D Committee meeting (RCO report). However, the R&D Chair may determine that an ad hoc or emergency meeting is in order.
- 4.2. Specific VA entities include;
- 4.2.1. VA Office of Research and Development if the study is VA-funded;
- 4.2.2. VA Privacy Office when the report involves unauthorized use, loss or disclosure of individually identifiable patient information;
- 4.2.3. VHA Information Security Officer when the report involves violations of VA information security requirements.
- 4.3. Other entities include but are not limited to the FDA, NIH, CDC, study sponsors, and funding agencies.
- 4.3.1. Applicable reporting procedures will be followed.

REFERENCES:

VAMHCS Policy Memorandum	512-001/OPS-010 Consumer Relations Program
IRB Policies and Procedures	All relevant policies & procedures
VHA Handbook 1058.01	“Research Compliance Reporting Requirements”
ORO Guidance	Office of Research Oversight (ORO) Guidance Regarding Research Compliance Officer (RCO) Research Audit Requirements for 2010 and 2011 (June 14, 2010)
ORO Checklist	Research Compliance Officer Checklist

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

ATTACHMENT 1: Examples of “Apparent” Serious or Continuing
Noncompliance
[VHA Handbook 1058.01 Par 5.f-g]

f. **Examples of Apparent Serious Noncompliance.** Examples of apparent serious noncompliance that must be reported to the IRB within 5 business days include, but are not limited to:

- (1) Any finding of noncompliance with human research requirements by any VA office (other than ORO) or any other Federal or state entity (e.g., FDA). Subsequent reports to ORO based on findings made by entities external to the facility must include a copy of the official findings.
- (2) Initiation of VA human subject research, regardless of level of risk or number of subjects, without written notification from the ACOS for Research that the project may begin.
- (3) Initiation of VA human subject research, regardless of level of risk or number of subjects, without approval by the IRB.
- (4) Initiation of research interactions or interventions with one or more subjects prior to obtaining required informed consent.
- (5) Lack of a required, signed informed consent document or lack of a required, signed Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule authorization for one or more subjects.
- (6) Use of an informed consent document, for one or more subjects, whose content was not approved by the IRB.
- (7) Failure to report one or more unanticipated SAEs or unanticipated serious problems involving risks to subjects or others as required by this Handbook.
- (8) Participation by one or more members of the research team in the conduct of an active protocol without the required credentialing, privileging, or scope of practice, or engaging in activities outside the approved scope of practice.
- (9) Continuation of interactions or interventions with human subjects beyond the specified IRB approval period.
- (10) Implementation of substantive protocol changes without IRB approval, except where necessary to prevent immediate hazard to a subject.
- (11) Involvement of prisoners or children in VA research, or conduct of international VA research, without the required approval by the VHA Chief Research and Development Officer (CRADO).
- (12) Any noncompliance involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;
- (13) Any noncompliance that substantively compromises the effectiveness of the facility’s human research protection or human research oversight programs.
- (14) Serious programmatic noncompliance. Examples include, but are not limited to:
 - (a) Conduct of IRB business by an improperly constituted committee or with less than a quorum of voting members present.
 - (b) Improper designation of research as exempt under 38 CFR 16.101(b).
 - (c) IRB approval of a waiver of informed consent, a waiver of documentation of informed consent, or a waiver of HIPAA Privacy Rule Authorization when the respective approval criteria at 38 CFR 16.116(c) or 16.116(d), 38 CFR 16.117(c), or 45 CFR 164.512(i)(1)(i) are not met or are not documented.

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

(d) Programmatic failure to provide for and document Privacy Officer (PO) and Information Security Officer (ISO) review of proposed human subject research.

(e) Any programmatic noncompliance involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;

(f) Any programmatic noncompliance that substantively compromises the effectiveness of the facility's human research protection or human research oversight programs.

g. **Examples of Apparent Continuing Noncompliance.** Examples of apparent continuing noncompliance that must be reported to the IRB within 5 business days include, but are not limited to:

(1) Failure to implement IRB-required changes to an on-going protocol within the time period specified by the IRB.

(2) Deficiencies in informed consent or HIPAA authorization procedures or documentation for ten or more subjects (e.g., outdated informed consent or HIPAA content; lack of required informed consent elements; lack of information required by VA; lack of signature of individual obtaining consent).

(3) Failure to maintain documentation required by the IRB or by the IRB-approved protocol for ten or more subjects (e.g., inadequate medical record documentation where required; inadequate case report forms where required).

(4) Failure to implement remedial actions within the periods specified at subparagraphs 5d(1) or 5d(2) in the absence of the justification described at subparagraph 5d(3).

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDUREATTACHMENT 2: Information Required for ORO Reports
[VHA Handbook 1058.01 Par 5.b-c]

b. **Contents of Initial Reports to ORO.** Initial reports to ORO of reportable research events must (as applicable) include:

- (1) The name and any relevant Assurance number of the reporting VA facility.
- (2) The title of the research project(s).
- (3) The number(s) used by the facility's Research Service or relevant research review committee(s) to identify the project(s).
- (4) The name of any external sponsor(s) of the project(s).
- (5) The funding source(s) for the project(s).
- (6) The name of any agencies or organizations external to VA that were notified, or need to be notified, of the event.
- (7) A description of the event being reported.
- (8) A description of any immediate actions taken to address or investigate the reported event.

c. **Contents of Follow-Up Reports to ORO.** After the initial report, additional investigation and review are frequently needed to obtain a complete understanding of the facts associated with the case. Interim and final reports must be provided as directed by ORO to incorporate the full scope of relevant determinations and remedial actions, including programmatic actions as warranted.