

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

Human Research Protection Program SOP #21

July 27, 2009

RESEARCH COMPLIANCE PROGRAM

1. POLICY

The Tuscaloosa VA Medical Center (TVAMC) Human Research Protection Program (HRPP) is committed to protecting the rights and welfare of human research subjects, ensuring the integrity of the HRPP, and preserving public trust in the integrity and quality of research carried out by its investigators and in its facilities. To do this, appropriate mechanisms must be in place to evaluate the functioning of the HRPP and the safeguards in place to protect human research subjects in VA research.

Auditing is a mechanism for evaluating TVAMC's human subject research program and, when appropriate, identifying areas for corrective action. An active auditing plan should provide reasonable assurance of the integrity of the research program and that adequate protections for research subjects are in place. To provide this reasonable assurance the staff conducting the audits must be independent of the research program and the research study.

It is the policy of the TVAMC HRPP to establish a Research Compliance program to assess, promote and ensure compliance with applicable laws, regulations and policies related to human subjects research. This Standard Operating Procedure (SOP) provides a written plan for random and periodic auditing activities to be followed by the Research Compliance Officer (RCO). Compliance monitoring improves research processes and provides internal oversight on quality and compliance issues relating to the performance of clinical research involving human subjects.

2. RESPONSIBILITIES

TVAMC Medical Center Director: The Director has ultimate responsibility for the Research Compliance program. The Director is the responsible for designating a Research Compliance Officer who

- Reports directly to the Medical Center Director
- Has the appropriate skills and knowledge to fulfill the responsibilities of the position
- Doesnot have collateral duties that create or have an appearance of conflict with research monitoring
- Has adequate resources to achieve the objectives of this policy.

In addition, the Director is responsible for evaluating, at least annually, the effectiveness of the auditing program.

Chief for Research and Development (C/R&D): The C/R&D is responsible for evaluating the overall R&D program for compliance with applicable regulations and for notifying the RCO of any reports of noncompliance or research impropriety.

Research Compliance Officer (RCO): The TVAMC RCO will report directly to the Medical Center Director and will not engage in research. The RCO is responsible for:

- developing and implementing a Research Compliance Program, including the policy for the auditing program
- conducting a complete audit of each VA-approved human research study, according to the schedule provided by the Office of Research Oversight, or as-needed
- conducting an audit of each VA-approved human research study for compliance with the regulations and policies on informed consent once a year
- ensuring that human subjects' study audits assess compliance with all applicable laws, statutes, regulations, and policies, including those related to privacy, confidentiality, and information security
- reporting non-compliance, as required, to the TVAMC IRB or directly to the Facility Director
- Providing a performance report at least quarterly to the Director

Investigators: Investigators are responsible for:

- maintaining all essential documents necessary to ensure that studies involving human subjects are conducted as specified in the protocol and approved by the IRB;
- making all essential documents available to the RCO for review upon request and within a reasonable time period, generally two weeks;
- reporting of self-identified non-compliance in accordance with TVAMC HRPP SOPs
- recommending and implementing action plans to address compliance problems.

3. DEFINITIONS OR CRITERIA

a. 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.

b. Completed study: A “completed” study is a study for which oversight by all relevant research oversight committees (see Item 1b above) has been concluded.

c. Human Subjects Research: Human subjects research is research that involves human subjects.

1. As defined in the Common Rule (38 CFR 16) and VHA Handbook 1200.05, a human subject is a living individual about whom an investigator conducting research obtains:

2. As defined in the Common Rule (38 CFR 16) and VHA Handbook 1200.05, a human subject is a living individual about whom an investigator conducting research obtains:
 - i. data through intervention or interaction with the individual, or
 - ii. identifiable private information.
 3. An intervention includes both physical procedures by which data are gathered and all manipulations (physical, psychological or environmental) of the human subject, or the subject's environment, that are performed for research purposes.
 4. Interaction includes communication or interpersonal contact between the investigator and the human subject.
 - i. data through intervention or interaction with the individual, or
 - ii. identifiable private information.
- d. Informed Consent Audit:** An RCO audit of all documents and documentation pertaining to the provision or waiver of informed consent, i.e., a process and written notification to human subjects involved in clinical investigations that provides them with sufficient opportunity to consider whether or not to participate in the study.
- e. Institutional Review Board (IRB):** The IRB is a board established in accordance with and for the purposes expressed in, the Federal Policy (Common Rule) for the Protection of Human Subjects (Title 38 Code of Federal Regulations (CFR) 16.102(g)). It is responsible for the review of, approval or disapproval of, and continuing oversight of research involving human subjects.
- f. Regulatory Audit:** An RCO audit that includes all essential documents, including regulatory documents and patient records, required to be maintained by the Principal Investigator to document that a study is performed in accordance with for a research study.
- g. Research:** As defined by the Common Rule (38 CFR 16.102(d)) research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- h. RCO audit:** RCO audits are audits conducted, supervised, or verified by the facility's lead RCO.

4. PROCEDURES

- a. Audit Plan:** Within 30 days after the start of a new reporting period beginning June 1 of each calendar year, the RCO will prepare an audit plan for the period. This plan will be submitted to the Medical Center Director for approval prior to the RCO's initiating any audits for the reporting period.

The plan will specify the criteria for all *mandatory* audits to be performed during the reporting period and provide projections for the number of informed consent audits and regulatory to be conducted annually and by calendar quarter. For regulatory audits, the

plan will include criteria for prioritizing those audits, along with any recommendations from the RCO for auditing specific studies, due to concerns about compliance or safety of participants.

In addition, the plan will acknowledge the RCO's responsibility for completing any audits required by competent third parties and any additional audits suggested by problems or concerns identified by the RCO, the IRB, the R&D Committee, or Medical Center Director during the period. Such audits may be recommended and undertaken either as a proactive measure to identify potential problems, as in studies with greater than minimal risk, and/or as a retrospective measure to ensure that prior solutions to problems, such as remedial plans for noncompliance in previous years, have been effective.

b. Audit Notification:

1. Routine (not-for-cause) Audits

The RCO will select the protocol to be audited and then contact the PI and study coordinator, if applicable, by email 1 – 2 weeks before the audit, notifying them that their protocol has been selected for a routine regulatory audit. The RCO will schedule a date and time for the audit within this time period that is convenient to the investigator. If the PI and/or study coordinator does not respond to the RCO within 3 business days, the RCO will follow-up with the PI by telephone. Once the date and time is determined, the RCO will send a confirmation email stating the date, time, expected length of time needed for the visit and the list of items the RCO expects to review. Investigators may request to reschedule *for appropriate reasons*. Except in extreme circumstances, audits will not be postponed for more than 30 days after initial notification.

2. For-Cause Audits

“For-cause” audits will be scheduled within a few days of the audit request. Notification to PI and the study coordinator, if applicable, will be via email (phone when required) to confirm a date and time for the audit. The Investigators must comply with the agreed upon date and time of the audit or notification will be forwarded to the IRB subcommittee. The PI or an individual designated by the PI may be present during the audit process. In instances where the PI chooses not to be present, a selected designee or someone associated with the project, must be available to answer questions that may arise during the audit.

3. Unannounced Audits

The RCO reserves the right to show up unannounced at any time to evaluate a specific issue, problem or process.

4. Notification and Scheduling Problems: If extenuating circumstance prevent the PI or his/her delegate from meeting with the RCO for a timely audit or if the PI does not provide access to the necessary documents, the RCO will notify the C/R&D in writing. If, after notifying the C/R&D, there is no resolution to scheduling or provision of document issues, the IRB Chair will be notified in writing, with

copies to the C/R&D and R&D Committee Chair. If the non-cooperating C/R&D is the PI, notification will be directly to the IRB with copies to the C/R&D and R&D Committee Chair.

c. Types of Audits:

1. **Informed Consent Audits:** Informed consent audits of all active human research studies must be performed each year (i.e., annually) and require a review of subjects' signed VA informed consent documents (where applicable). The annual informed consent audit requirement includes human studies determined to be *exempt* from IRB review. The audit requirement is fulfilled by confirming and documenting that the IRB approved the exemption and documented which exempt category applied for any active IRB-exempt study. The template for informed consent audits is provided as an attachment.

i. **Informed consent audits for the January 1, 2009 – May 31, 2009, reporting period.** All human research studies active at any time between January 1, 2009 and May 31, 2009 must receive an informed consent audit. The informed consent audit must include informed consent *documents* (where applicable) obtained within 12 months prior to the date of the audit. In addition:

A final informed consent audit must be conducted for any study completed between January 1, 2009, and May 31, 2009.

NOTE: A study audited during the reporting period will require a supplemental audit if the study was completed before the end of the reporting period (i.e., before May 31, 2009) and additional informed consent documents were obtained after the audit.

Informed consent audits for the January 1 through May 31, 2009 audit period must be completed in time to be included in the 2009 Facility Director Certification of Research oversight, which must be submitted through the Network Director to ORO Regional Offices and received by ORO no later than July 15, 2009.

ii. **Informed consent audits for reporting periods beginning June 1, 2009, period.** All human subjects research studies active at any time between June 1, of any year beginning in 2009 and ending on May 31, of the following year (e.g., June 1, 2009 – May 31, 2010) must receive an annual informed consent audit. For these reporting periods studies that *were not* audited previously must include all informed consent documents obtained within 12 months prior to the date of the audit, and studies that *were* audited previously must include all informed consent audits obtained since the previous audit.

A final informed consent audit must be conducted for any study completed between June 1, of any year beginning in 2009 and ending on May 31, of the following year. *NOTE:* A study audited during the reporting period will require a supplemental audit if the study is completed before

the end of the reporting period and additional informed consent documents are obtained after the audit.

Informed consent audits for these reporting periods must be completed in time to be included in the Facility Director Certification of Research Oversight for the year in which the audit period ended. The Certification must be submitted through the Network Director to ORO Regional Offices for receipt by ORO no later than July 15 of that year.

2. Regulatory audits. Except as noted below, regulatory audits of human research studies initiated after January 1, 2008, must be performed at least every three years (i.e., triennially) and require review of case records and regulatory files. Routine regulatory audits are not required for (a) any study determined to be *exempt* from IRB review; (b) any study initiated (i.e., approved for implementation as a VA study) prior to January 1, 2008; or (c) any study completed prior to June 1, 2009. Research studies of less than three (3) years duration must be audited at least once during the study.

Periodic audits may, at the discretion of the RCO, be conducted more frequently than every third year. Increased frequency of audits may be justified where, for example, (a) serious or repeated noncompliance has been identified in a research project of the practices of an individual researcher, (b) required by changes in VA policy; (c) directed by authorities, such as the IRB or a study Sponsor; (d) vulnerable populations are involved; (e) level of risk is greater than minimal; (f) studies use FDA approved drugs for which there has been a safety warning or change in labeling indicating increased risk; a data breach has occurred.

- i. Regulatory audits for the January 1 – May 31, 2009, reporting period. No regulatory audits are required for the January 1, 2009, through May 31, 2009, reporting period.

Any regulatory audits performed during the January 1 through May 31, 2009, reporting period should be included in the 2009 Facility Director Certification of Research Oversight, which must be submitted to ORO Regional Offices through the Network Director and received by ORO no later than July 15, 2009

- ii. Regulatory audits for reporting periods beginning June 1, 2009. Except as noted above, regulatory audits are required for all human subjects research studies completed between June 1, of any year beginning in 2009, and ending on May 31 of the following year (e.g., June 1, 2009 – May 31, 2010). Approximately 33% of human subjects research studies initiated after January 1, 2008, should receive a regulatory audit in the June 1, 2009, through May 31, 2010 reporting period, and in each future reporting period, in anticipation of satisfying the triennial audit requirement.

Regulatory audits for reporting periods beginning with the June 1, 2009 – May 31, 2010 reporting period must be completed in time to be included in the Facility Director Certification of Research Oversight for that year, which must be submitted to ORO Regional Offices through the Network Director and received by ORO no later than July 15, of that year.

The template for routine human research regulatory audits is provided as an attachment.

3. For cause audits: For cause audits will be conducted on an “as needed” basis, often at the request of a Sponsor or the IRB. These audits may be broad or may be focused on a specific issue. These audits will not be reflected in the annual Facility Director Certification of Research Oversight unless the audited studies would otherwise have been included in an informed consent audit or regulatory audit for the reporting period.

Issues of noncompliance, unanticipated problems involving risk to subjects or others, or adverse events discovered during the conduct of any audit (routine or for-cause) will be reported according to the requirements of *HRPP SOP #18: Complaints, Allegations or Findings of Noncompliance and Reporting Requirements* and *VHA Handbook 1058.01: Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight*.

- d. Conduct of the Audits:** The RCO will meet with the PI or an individual designated by the PI at the scheduled time. The PI or his/her designee may be present during the audit process. In instances where the PI chooses not to be present, a selected designee or someone associated with the project must be available to answer questions that may arise during the audit.

NOTE: In the event of a real or apparent conflict of interest on the part of the RCO, the VISN 7 RCO will conduct the audit or designate another facility RCO to perform the audit.

At the beginning of the audit, the RCO will meet with the PI or designee to:

- review the purpose of the audit, including the items that will be reviewed
- complete a sign-in sheet indicating the date of the audit, the name of the study being audited, the person with whom the RCO met, and a statement that the purpose of the audit was explained.

The RCO will examine the Essential Documents for the study to review all required documentation. It is understood that all documents will not be kept in one binder. The types of documents subject to review include regulatory documents, (including subject logs and Sponsor protocol, if these are kept separately), operations manual(s), case report forms and patient records. Electronic medical records may be reviewed as needed. If required documentation is not locate, the RCO will ask the PI or representative to help locate documents before assuming that they were not

completed. *NOTE: Some essential documents (e.g., pharmacy records) may be retained in a separate location and may need to be reviewed as part of the audit.*

Following completion of the audit, the RCO will:

- provide a brief oral report to the PI or designee of findings and recommendations
- complete the bottom portion of the sign-in form indicating if there were major findings
- within 3 business days, send a brief written report to the PI with a copy to the designee and/or study coordinator, if applicable.

e. Areas Subject to Audit: The RCO will audit all compliance aspects of a study. For individual studies areas that may be audited, as required, include

- Regulatory Compliance (including all regulatory (essential) documents, case report forms and source documents)
- Adverse event reporting
- Inclusion and Exclusion Criteria
- Documentation of Informed Consent
- Waiver of informed consent and the required documentation by the IRB
- Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant authorization
- Waiver of HIPAA compliant authorization and the required documentation by the IRB
- Compliance with all data security and data use requirements
- Compliance with all confidentiality requirements
- Compliance with all privacy policy requirements
- Adequacy of HRPP
- The informed consent process (i.e., the RCO may witness the process)

f. Reporting Possible Noncompliance:

1. The procedure for reporting serious or continuing non-compliance found during an RCO audit is different from the procedure for reporting serious or continuing non-compliance identified in other ways (e.g., investigator self-reporting to the IRB, as described in *HRPP SOP #18: Complaints, Allegations or Findings of Noncompliance and Reporting Requirements*). All instructions for reporting issues related to research compliance will be consistent with VHA Handbook 1058.01: *Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight*.
2. If an RCO identifies apparent serious or continuing non-compliance during the conduct of an audit, the RCO will conduct an investigation to confirm the facts of what occurs and will prepare a written report:
 - a. To be submitted as soon as possible, but not later than 5 days.
 - b. To be sent to the Facility Director, the Chairperson of the IRB, the Chairperson of the R&D Committee and the Chief/ R&D
 - c. To include the following information:

- Project name and identification number assigned by the IRB
- Principal investigator (PI)
- Detailed description of the event being reported
- Detailed description of any actions that have been taken by the PI to address the compliance problem

3. **Examples** of noncompliance

The following are *examples* of noncompliance that might be identified during an audit and that should be reported in the 5-day timelines described above:

- Lack of a signed informed consent document in a study where informed consent or documentation of consent has not been waived
- Lack of signed Health Insurance Portability and Accountability Act (HIPAA) Authorization in a study where HIPAA authorization has not been waived
- Repeated use of an unapproved, unstamped, or outdated informed consent document (either in a single study or by the same investigator across studies)
- Repeated failure to obtain the signature or signature dates of the witness or of the individual obtaining consent
- Lack of IRB approval before initiating research activities
- Initiating research procedures with a person before obtaining consent
- Initiating substantive protocol amendments without IRB approval, unless necessary to prevent immediate hazard to the subject.
- Ignoring IRB, R&DC, or other oversight committee requirements, such as the requirement to submit a request for continuing review

NOTE: These examples are not intended to provide a comprehensive list of the types of noncompliance that might be identified and/or require reporting in the 5-day timelines described above.

4. Following receipt of the RCO report, the IRB Chair or designee may investigate further and to take any action necessary to protect human subjects (i.e., suspend, terminate, place study on administrative hold). The Chair will report the findings to the convened IRB, or the Chair may delegate this responsibility to the RCO or another designated individual. The IRB will reviews the report of non-compliance pursuant to *HRPP SOP #18: Complaints, Allegations or Findings of Noncompliance and Reporting Requirements* and determine whether the noncompliance was actually serious or continuing, and what corrective actions are needed. The R&D Committee would be the responsible committee for issues related to safety.
5. The RCO will be available for consultation with the PI, the IRB Chair and the R&D Committee Chair for consultation about corrective action plans. However, final decisions about what constitutes an appropriate remedy rest with the IRB (or R&D Committee for issues related to safety).

6. Because the RCO reports simultaneously to the Facility Director and the Chairpersons of the IRB and R&D Committee, the events reported represent probable serious or continuing non-compliance. At the time of the initial report, a full assessment and committee determination concerning the report will not have been made by the IRB (or R&D Committee). However, the initial report must be made within the 5-day timeframe described above.
7. Within 5 business days of receiving a report of apparent serious or continuing noncompliance, the Facility Director will submit an initial report to ORO, ORD and the VISN in accordance with VHA 1058.01: Requirements for Reporting Research Events to Facility Oversight Committees and the Office of Research Oversight. Copies of the Director's report will be sent to the C/R&D, the IRB Chair and R&D Committee Chair. If reports to other agencies or organizations are required, these will be submitted within the time frame required by the entity receiving the report (see also *HRPP SOP #18: Complaints, Allegations or Findings of Noncompliance and Reporting Requirements*). The RCO will provide timely information to assist the Facility Director in preparing reports and will maintain a file of compliance-related reports and correspondence.
8. Following the initial report to ORO of probably serious or continuing non-compliance, ORO may request periodic updates from the facility until determinations of corrective actions are finalized and documented. The RCO is responsible for ensuring that remediation plans are communicated to ORO.
9. The RCO will participate in the monitoring and evaluation of the corrective actions through follow-up audits and reporting.

NOTE: The RCO will audit all aspects of a study, including the PIs response to IRB requirements and the timeliness of that response.

A flow chart outlining the process for reporting noncompliance is included as an attachment to this policy.

- g. Annual Certification of Audits:** As part of the annual Facility Director's Certification of Research Oversight, the RCO will complete the summary page reporting the number and types of studies that were active during the reporting period, the number of studies receiving informed consent and regulatory audits, and the number of compliance problems that were reported during the year.

The Research Compliance Officer, along with the C/R&D and R&D Administrative Officer, will cooperate in obtaining documentation needed to complete the remainder of the Annual Certification, contacting others within the TVAMC as needed, such as HR (for verification of credentialing) and the ISO (for verification of compliance with data security questions). Final versions of the report will be routed through the C/R&D and the Chief of Staff for review, comment and approval. The Facility Director will be responsible for certifying the report and submitting it in accordance with directions provided annually by ORO.

- h. Facility Reports:** The RCO will meet with research personnel and facility staff upon request to disseminate new compliance policies, trends observed during compliance audits, needs assessments and interim progress reports.
- i. Audits of Other Research Processes:** The RCO will provide reports to the R&D Committee based on the following process audits, conducted as part of the HRPP compliance and quality improvement (CQI) program as described in *HRPP SOP #9A: Financial and Nonfinancial Conflict of Interest and SOP #17: Compliance and Quality Improvement*. These CQI efforts may include audits of (1) committee members' financial disclosure/conflict of interest; (2) compliance with mandatory training; (3) IRB minutes; (4) IRB performance; (5) investigator performance.

5. REFERENCES

- VA Directives 2008-064, 2006-067 and 2008-059
- VHA Handbook 1058.01, 1100.19, 1200.05, 1200.08, 1605.1
- 38 CFR 16

6. ATTACHMENTS

- Informed Consent Audit Template
- Regulatory Audit Template
- Flow Chart for Reporting Noncompliance
- Annual Certification of Audits

7. REVIEW DATE

January 1, 2012

Signature on File in R&D Office

Lori L. Davis, MD

Chief of Research and Development