North Florida / South Georgia Veterans Health System

Designing the Regulatory Structure of a Human Research Study

The goal of this document is to 1) assist investigators with understanding the regulations that affect VA research, and guide the administrative planning process to abide by those regulations; 2) alert investigators to potential pitfalls in the study approval process, and provide guidance for resolving those issues early and in parallel; 3) optimize the efficiency of initiating and revising studies; and 4) encourage productive communication among all parties by referencing VA Handbooks, Directives, and user guides.
Investigators are strongly encouraged to contact Research Service administrators with any questions. This guidance document will be updated over time, as new situations arise and/or new information becomes available.
Additional helpful information for VA researchers is located on the Research Service website:
https://www.nffre-research.org/va-research-resources

A message from the ACOS/Research and DCOS/Research

Many people who pursue careers in medical research do so to fulfill a love of science, and to help patients overcome disease and functional limitations. However, along with those important goals is the need to follow a variety of regulations that ensure responsible conduct of research. There are multiple oversight boards and personnel including the Institutional Review Board (IRB), Human Research Protections Program (HRPP), Subcommittee on Research Safety (SRS), Research Compliance Officers (RCO), Privacy Officers (PO), and Information Security Officers (ISSO). The RCO, PO, and ISSO are independent of VA Research Service, to ensure objective oversight. Researchers should understand that oversight boards/personnel provide a service to your research program, including by protecting you from liability, helping research administration run smoothly, protecting patient safety and privacy, and safeguarding your data. Please be mindful to respond promptly and politely to emails or phone calls received from research oversight personnel. In addition, please make an effort to learn and follow applicable regulations. Cooperation in these aspects of research will make for a more collegial, productive, and pleasant experience for everyone involved.

Consistency and completeness are key

• A common cause of delay in study approval is issues with consistency and/or completeness of documents submitted to the IRB, HRPP, Privacy Officer, and Information Security Officer.
• When an inconsistency is found, the study bounces back to the research team and then must be re-submitted for re-review to the appropriate board or officer. Resolving inconsistencies can add days or even weeks to the approval process.
• The PI and study staff should consider creating a spreadsheet for internal tracking, to ensure that important elements of the study are included and consistent across the Protocol, Informed Consent Form, HIPAA Authorization, Enterprise Research Data Security Plan (ERDSP), IRB web forms, and any other applicable documents.

Consider citing the regulations in your study approval documents

• You can help simplify the review process by citing the source of regulatory information (e.g., VA Handbooks, Directives, and user guides) that supports any potentially contentious issue that could arise during the review of your study. This practice is demonstrated throughout the present document.
• Citing the regulations will help to prevent people from talking past each other, and instead builds consensus by ensuring that all parties are reading the same pertinent regulatory sentences/paragraphs.

Who can be a VA Principal Investigator or a Co/Sub-Investigator?

• An individual who is included as an investigator (PI or Co/Sub-I) on a funding application should also be included as an investigator on the subsequent IRB submission. Individuals not included on a funding application may be listed as an investigator or a different role (e.g., "Other") on the IRB submission. Anyone listed as an investigator must adhere to the regulations described below.
• All investigators (PI or Co/Sub-I) must have the appropriate training, education, expertise, and credentials to conduct the research according to the research protocol. Investigators must be identified on the IRB application and must provide credentials, conflict of interest statements, or other documentation required by VA and local facility policies.
• Local policy requires that a resume/CV explaining training, education, expertise, and credentials pertinent to the research should be uploaded annually to each investigator's profile in IRBNet/VAIRRS.
• All investigators must hold a current VA appointment. Investigators can be full-time or part-time employees, however Principal Investigators with funding from the VA Office of Research and Development must have at least a 5/8ths VA appointment.
• Without compensation (WOC) employees and Interagency Personnel Act (IPA) employees are permitted to serve as an investigator, including Principal Investigator.
• Clinicians who serve as investigators should have a written acknowledgment signed by their Service/Section Chief and the Chief of Staff. This acknowledgment should address protected research time. In the absence of protected research time, clinicians should hold a without compensation (WOC) appointment to conduct research outside of their clinical tour of duty.
• Individuals who are responsible for implementing a VA contract or who work under a VA contract cannot have a VA appointment, because this creates a financial conflict of interest. This means that contracted personnel cannot be VA investigators or WOCs.
• Trainees are not permitted to serve as Principal Investigators. However, trainees may serve as a co- or sub-investigator (see the section on trainee research for more information).

Useful References:

• *VHA Directive 1200.05, Requirements for the Protection of Human Subjects in Research*
• *VHA Directive 1200.02, Section 10: Research Business Operations; Trainee Research*

Is your project considered trainee research, such as a doctoral dissertation?

• See VHA Directive 1200.02, Section 10 pertaining to Trainee Research. Trainees are not permitted to serve as VA Research Principal Investigators. However, trainees may serve as a co- or sub-investigator if a VA Investigator sufficiently experienced in the trainee's research topic is willing to serve as the PI.
• Trainees must be enrolled in an accredited training program sponsored by an affiliated educational institution under a current academic affiliation agreement with NF/SGVHS. Students from unaffiliated academic institutions in the community may not be permitted to conduct student projects in VA or be given a WOC appointment for the sole purpose of conducting student research. For inquiries about setting up a new academic affiliation with NF/SGVHS, contact the Associate Chief of Staff for Education.
• A doctoral dissertation is always considered research because the work is being done to fulfill the requirements of a research degree and to broaden knowledge in the field (i.e., unlike a quality improvement project that is intended to improve processes only within the VA). This determination has been made by the ORD Director of Regulatory Affairs.
• A trainee who also happens to be a clinician employee with NF/SGVHS does not have special privileges for use of VA data or resources. Trainee research cannot be conducted during the employee's clinical tour of duty,

unless protected research time is granted by the Service Chief and Chief of Staff. Rather, trainee research must be conducted during off-duty hours under a "without compensation" (WOC) appointment.

Useful References:

- *VHA Directive 1200.02, Section 10: Research Business Operations; Trainee Research*
- *Program Guide 1200.21: VHA Operations Activities That May Constitute Research*

Do study team members have real or perceived financial conflicts of interest (FCOI)?

- Federal employees are prohibited from participating in official VA matters affecting their own financial interest. A real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings.
- Whether or not a FCOI exists, all investigators on a project must complete a FCOI disclosure form annually in the "My COI" portal of IRBNet/VAIRRS (which is an electronic version of OGE Form 450 Alternative-VA).
- Other research staff (coordinators, etc.) are not required to complete a FCOI disclosure. However, if a real or perceived FCOI exists for any staff member involved in the study, it is best practice is to submit a disclosure.
- FCOIs must be reviewed by the Office of General Counsel. Depending on the complexity of the situation, this may add time to the study approval process and/or may require adjustments to avoid the FCOI.

Useful References:

- *OGE FORM 450 Alternative-VA*

Do you need to hire staff for your study?

- Please begin the hiring process immediately upon receiving notification that the sponsor intends to fund your study. Hiring of VA employees can take several months. Studies submitted/funded through NFFRE (i.e., studies with non-VA funding sources) are usually able to hire staff more quickly.
- If you need advice about how to advertise for staff members, please contact the Associate Chief of Staff for Research and/or Deputy Chief of Staff for Research.

Which Institutional Review Board will oversee your study?

- The Malcom Randall VA Medical Center (MRVAMC) does not have an internal IRB, but rather can use multiple different external IRBs depending on the circumstances. These are our "IRBs of Record" covered by our Federalwide Assurance (FWA): University of Florida (UF) IRB, VA Central IRB (VA CIRB), Western IRB – Copernicus Group (WCG IRB), Advarra IRB, and National Cancer Institute Central IRB (NCI CIRB).
- Single site studies conducted at MRVAMC (or collaborative studies between MRVAMC and UF) usually use the UF IRB. In unusual cases a different IRB might be used, such as if a commercial IRB is the IRB of record for a sponsored study.
- Multi-site studies: Use of a single IRB is required for non-exempt human studies with more than one institution engaged in the research (unless a single IRB exemption is granted by ORD).
    - If the multi-site research is funded by the VA (such as the VA Cooperative Studies Program), then CIRB must be used. An exception is if the only two sites are MRVAMC and UF, in which case the UF IRB can be used. UF IRB cannot serve as the single IRB for studies with multiple VA sites, because UF is not an approved IRB of Record for any VA except MRVAMC.
    - If the multi-site research is funded by a non-VA source, then UF IRB can be used (or a commercial IRB; WCG IRB or Advarra, if the study sponsor is utilizing their services).
- Industry sponsored trials can use any of the IRBs, depending on the circumstances. For single-site industry trials the UF IRB can be used, or a commercial IRB can be used if the sponsor has already engaged that IRB. For

multi-site industry trials, a commercial IRB would generally be used. But the UF IRB could be used if a single-IRB exception is granted. Industry sponsored trials can also use VA Central IRB in some cases.
• ORD-approved expanded access ("compassionate use") studies can use UF IRB or WCG IRB.
Useful References:
• *VHA Directive 1200.05:* REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH (please search Directive 1200.05 for keyword "IRB of record" and "IRB(s) of record").
• *https://www.research.va.gov/programs/orppe/single_irb.cfm*

Will you share data with an outside organization, and/or store data on a non-VA system?

• The ability to store de-identified, coded, or identifiable data on an external system depends on the specific wording of the approved HIPAA Authorization and the specific wording of any approved agreements (contract, CRADA, DUA, DTA, etc.) pertaining to the study. See below for more information.
• You must include the outside organization as a "disclosure" on the HIPAA Authorization form (10-0493). See VHA Directive 1605.01, Section 13. Research.
• You may need to request an Authority to Operate (ATO) to use the external system.
• You may need to submit a Data Use Agreement (DUA) to describe the terms of data use and storage.
However, data may be disclosed *without* a DUA to a non-VA individual or entity if it is for research purposes and a signed research informed consent and signed HIPAA authorization has been obtained from each research subject. See VHA Handbook 1200.12, Appendix C, Section 2c.
• Some external systems already have regulatory language within existing financial contracts through Malcom Randall VA Medical Center, which may provide information regarding data use and protections. For example, the BRRC has existing contracts with UF Computing (for data storage) and with UF AMRIS (for MRI acquisition and data use).
• Storage of identifiable data on external systems requires a waiver from the VA Chief Information Officer (VHA Directive 1605.01, Section 13. Research, Paragraph 13). Otherwise, only de-identified data (or coded data without the linkage information) should be placed on external systems of collaborating organizations.
• If there is no agreement in place that restricts the external organization's use/disclosure of the information (e.g., optional language within a contract, DUA, memorandum, etc.), then ownership of the disclosed data transfers to the recipient and VA cedes control over the information (VHA Directive 1605.01, Section 13. Research, Paragraph 13). VA regulations would no longer apply to the disclosed data.
Useful References:
• *VHA Directive 1080.01: DATA USE AGREEMENTS*
• *VHA Handbook 1200.12: USE OF DATA AND DATA REPOSITORIES IN VHA RESEARCH*
  ◦ *APPENDIX B: THE EIGHTEEN HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 (HIPAA) IDENTIFIERS*
  ◦ *APPENDIX C: COMBINED DATA USE DATA TRANSFER AGREEMENT REQUIREMENTS*
• *VHA Directive 1605.01: PRIVACY AND RELEASE OF INFORMATION*
• *ERDSP Guide[1]: section on "External Information Systems and Data Sharing with non-VA Entities"*

Will you collect data at a non-VA site?

• If the study is administered by the VA or NFFRE, you will need a full or partial off-site waiver.
• Staff at the non-VA site must be covered by a VA agreement or appointments, such as a contract, cooperative research and development agreement, interagency personnel act (IPA) agreement, or without compensation (WOC) appointment. Individuals who are responsible for implementing a VA contract or who work under a VA contract cannot have a VA appointment, because this creates a financial conflict of interest. This means that contracted personnel cannot be VA investigators or WOCs.

• Caution: if a contract or IPA ends but the non-VA site is still engaged in VA research, this is a problem. The remote site would be conducting VA research with no agreements in place. For example, there is a high risk of this happening during a no-cost extension year. The solution is to make sure that VA research activities end before the contract/IPA expires, or to set up a WOC appointment for non-VA personnel before the contract/IPA expires.
• For studies originating outside the VA (i.e., VA is a secondary research site), it might make sense to create an entirely separate IRB/HRPP submission for the portion of the work being conducted at the VA. Although this may sound like extra work, the clean division between VA and non-VA research activities may reduce administrative burden and confusion in the long run. For example, study visits occurring at VA and non-VA sites should have separate informed consent forms, because there will be different regulatory language pertaining to participant injury, payments, and data privacy. Similarly, VA information security regulations differ from non-VA institutions, so filling out the ERDSP form will be confusing if the VA and non-VA research components are not clearly separated.
Useful References:
https://www.research.va.gov/resources/policies/ProgramGuide-Off-site-Research-1200-16.pdf

Are you working with an external organization that will require funding to conduct their research duties?

• You may need to set up a financial Contract. Contracts can take several months to set up, so begin this process immediately upon receiving notification that the sponsor intends to fund your study.

Are you working with an external organization on research that might lead to a patent or invention?

• You may need to set up a Cooperative & Development Agreement (CRADA). A CRADA is a written agreement between VA and one or more non-federal parties to work together on a research project. The CRADA defines the terms by which the VA may accept or provide personnel, services, facilities, intellectual property, equipment, and other resources. If VA funding is required, VA must go through the acquisition and procurement channels.
• Depending on the circumstances, you may need to disclose a financial conflict of interest (FCOI).

Useful References:
VHA Directive 1206: USE OF A COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

Will you use an external collaborator's electronic informed consent process?

Useful References:
• *ERDSP Guide[1]: section on "External Information Systems and Data Sharing with non-VA Entities"*

Will you share bio-specimens with an external organization?

• You may need to set up a Material Transfer Agreement
Useful References:
https://www.research.va.gov/resources/policies/guidance/draft-mta-guidance.pdf

Will you use a medical device that is intended to diagnose or treat patients, or that affects the body structure or function of a person or animal?

Useful References:
• *"Guidance on Medical and Investigational Devices", located on the Research Service website: https://www.nffre-research.org/va-research-resources*
• *VHA Directive 6550: PRE-PROCUREMENT ASSESSMENT AND IMPLEMENTATION OF MEDICAL DEVICES/SYSTEMS*

Will you use a mobile/wearable device or a portable storage device?

• Mobile devices (laptops, hard drives, thumb drives, etc.) should be encrypted with FIPS 140-2 validated encryption, or its successor.
• A plan must be described to back up data from mobile and portable devices to prevent data loss.
• Mobile devices may have privacy or information security risks that must be addressed.
• Research sponsors' and collaborators' mobile applications can be used to collect data from VA research subjects if the data collected by the sponsor or collaborators' mobile application is not owned by the VA. (Also see the section above on data sharing and storage to external organizations, with regard to data ownership.)
Useful References:
• *ERDSP Guide[1]: section on "VA Mobile Devices, Applications and Portable Storage Devices"*
• *ERDSP Guide[1]: section on "External Information Systems and Data Sharing with External Entities"*

Will you recruit or screen potential participants using medical record review, mailings, or telephone?

• You may need a "waiver of HIPAA authorization", "waiver of informed consent" and/or "waiver of documentation of informed consent" (please search Directive 1200.05 for keyword "waiver").
• There are regulations about how initial contact with potential research participants can take place (please search Directive 1200.05 for keyword "telephone").
• VA patients can be recruited to research studies using the VA Informatics and Computing Infrastructure (VINCI), specifically the Data Access Request Tracker (DART) application.
Useful References:
• *VHA Directive 1200.05:* REQUIREMENTS FOR THE PROTECTION OF HUMAN SUBJECTS IN RESEARCH
• *VINCI DART: https://www.nffre-research.org/_files/ugd/1aa558_e8da0a019adb463094bcbb41040977bf.pdf*

Will you be sending identifiable information via email?

Useful References:
• *https://www.research.va.gov/resources/policies/guidance/FAQs-Azure-RMS.pdf*

Will you be connected a research scientific computing device to the VA network?

• Network-connected research scientific computing devices must undergo a risk assessment.
Useful References:
• *ERDSP Guide[1]: section on "Data Sources and Collection"*

Will you be collecting data to a standalone (non-networked) computer?

• A plan must be described to back up data from stand-alone computer to prevent data loss.
Useful References:
• *ERDSP Guide[1]: section on "Data Access and Storage"*

Will you need to install software on a VA networked computer?

• The software may need to be evaluated by the VA Technical Reference Model.

Useful References:

• *ERDSP Guide*[1]*: section on "VA Software"*

Will your study involve medications/drugs in humans?

• Any chemical or biological compound being studied in a clinical investigation could be considered an investigational drug (or "study drug") – even an approved drug being studied for approved use. The interpretation depends on the parameters of the study.

• Studies involving medications/drugs usually require review by the Investigational Drug Service, and must complete VA form 10-9012.

• Any study using medications/drugs should seek guidance as early as possible from Research Pharmacist Alan Mumford at Alan.Mumford@va.gov

Endnotes

[1]The *Enterprise Research Data Security Plan (ERDSP) User Guide* is located on the IRBNet/VAIRRS website (gov.irbnet.org) in the library called "VHA ORPPE&E, Washington, DC – Documents for Human Subjects Researchers".