

**OFFICE OF RESEARCH AND DEVELOPMENT
VETERANS HEALTH ADMINISTRATION**

ORD Guidance on Approval of International Research

Date: October 20, 2014

SCOPE: VA international research is defined as any VA-approved research conducted at international sites (i.e., not within the United States (US), its territories, or Commonwealths), any VA-approved research using either human biological specimens or human data originating from international sites, or any VA-approved research that entails sending such specimens or data out of the US. *NOTE: Research conducted at U.S. military bases, ships, or embassies is not considered international research.*

This definition applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including MOUs, Cooperative Research and Development Agreements (CRADA), grants, contracts, or other agreements.

International research includes multi-site trials involving non-US sites where VA is the study sponsor, a VA investigator is the overall study-wide PI, VA holds the IND, or the VA manages the data collection and the data analyses. International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator (i.e., the PI for the study as a whole is not a VA investigator).

Sending specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA investigator on sabbatical at an international site) is considered international research.

Remote use of data that is maintained on VA computers within the United States or Puerto Rico and accessed via a secure connection is not considered international research.

This guidance is to assist IRBs, R&D Committees, and facility Directors in their review and approval of VA research that meets the definition of international research.

1. Under what circumstances can international research be approved in VA?
2. What information should be provided in a research proposal and/or review materials that involve international site(s)?
3. Are there additional requirements for research involving human subjects?
4. What should the VA IRB of record review and document for international site participation?
5. What should the R&D Committee review and document for international site participation?
6. What are the requirements for the facility Director memo of approval?
7. What is the process for CSP studies?

1. Under what circumstances can international research be approved in VA?

- The research should be relevant to VA's mission and the care of Veterans, or
 - is directly relevant to VA's role as a health care provider in a period of local or national emergency, or

- supports the mission of another Federal agency (e.g. DoD or NIH) through an interagency agreement or similar mechanism
- There should be adequate protection of human subjects (including privacy and confidentiality), and the implementation of adequate safety measures for research subjects and personnel.
- There should be appropriate security of VA data and VA sensitive information and storage of data and specimens in accordance with all applicable VA requirements.
- The investigators should comply with the applicable VA policies related to the identification and resolution of conflicts of interest of research personnel.
- All data should be obtained in accordance with international ethics rules and regulations pertaining to human research subjects and consistent with FR Vol. 70, No. 57, pp15322-15327, March 25, 2005 "Protection of Human Subjects, Proposed Criteria for Determinations of Equivalent Protections". .
- All international sites should hold an international Federal Wide Assurance (FWA).
- The research should be approved by the IRB or Research Ethics Board of the participating site(s) that are listed on the international FWA.

2. What information should be provided in a research proposal and/or review materials that involve international site(s)?

- Rationale for conducting the research at an international site(s), including why it cannot be conducted at a VA facility or within the United States. If the research involves a partnership between the VA and an international site, the rationale for this partnership and its benefits to the VA and the U.S. veteran population should be discussed.
- For each domestic and international site, any financial arrangements including funding source, any type of payment to subjects, and financial arrangements involving the research site and local investigators at the research site.
- Discussion of each site in the foreign country(ies) including the foreign investigator(s), the location(s), and a description of the facility(ies) where the research will be conducted.
- Any research assurances that are in place at the international site(s), including an International (Non-U.S.) Assurance issued by Office of Human Research Protections (OHRP).
- Copy(ies) of all approvals required by the foreign country(ies) and institution(s). Include information on the IRB or ethics board or other review board that has been established to ensure the ethical conduct of the research and any stipulations of the board(s) that were required to be addressed prior to the initiation of the research in that country.
- Information on how the U.S. VA IRB of record and the foreign IRB decisions will be communicated and reconciled if necessary.

- Information on VA's liability in relationship to the conduct of the research including a discussion on care for research-related injuries and any compensation available for subjects or others at the site because of research-related injuries.
- A plan for conducting oversight of the research to ensure ethical conduct, compliance with all applicable regulations, and validity of the data. The plan should include oversight by any foreign country or entity.
- Frequency and content of monitoring reports, including information on who will review the reports and make any determinations regarding safety of subjects and compliance with applicable regulations.

3. Are there additional requirements for research involving human subjects from the international site(s)?

- **Human Subjects Involvement and Characteristics.** Describe the proposed involvement of human subjects in the Research Design and Methods section. Describe the characteristics of the subject population, including their anticipated number, age range, and health status. Identify the criteria for inclusion or exclusion of any subpopulation. Explain the rationale for the involvement of special classes of subjects, such as pregnant women, institutionalized individuals, or others who may be considered vulnerable populations.
- **Sources of Materials if Other than the Research Subject Used in the Protocol.**
 - Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data, including information on research material that is obtained about deceased individuals or that is de-identified. Indicate whether the material or data will be obtained specifically for research purposes, or whether use will be made of existing specimens, records, or data.
 - If the materials are obtained for research purposes, explain how they will be collected, which ethics review body(ies) reviewed the collection and use of the materials, and by what standards.
 - If the material will be or has been collected for non-research purposes, describe the circumstance or reason for the collection.
- **Potential Risks.** Describe the potential risks to subjects (physical, psychological, social, legal, or other) and their likelihood and seriousness to the subjects. Differentiate therapeutic risk from research risk as follows:
 - Therapeutic risk is the risk or potential risks associated with an intervention that is required for medical care, but occurs as part of the research. An example is an endoscopy that was required for medical follow-up of a specific illness.
 - Research risk is associated with an intervention that is done only for research purposes regardless if it is an experimental intervention or a commonly used intervention, for example, an extra endoscopy. Where appropriate, describe

alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

- **Recruitment and Informed Consent.** Describe plans for the recruitment of subjects and the process for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent.
- **Protection Against Risk.** Describe the planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. For interventional studies, describe the plan for subject data and safety monitoring.
- **Potential Benefit of the Proposed Research to the Subject and Others.** Discuss the potential benefits of the research to the subjects and others, including why the risks are reasonable in relation to the anticipated benefits.
- **Importance of the Knowledge to Be Gained.** Discuss the importance of the knowledge to be gained as a result of the proposed research, including why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

4. What should the VA IRB of record review and document for international site participation?

- The VA IRB of record should review the research proposal and additional materials to determine that all criteria for IRB approval have been satisfied in accordance with VHA Handbook 1200.05.
- Review and approve consent documents in accordance with VHA Handbook 1200.05, or waiver of consent or documentation of consent if these criteria are met.
- Assure that appropriate research assurances are in place at the international site(s), including an International (Non-U.S.) Assurance issued by Office of Human Research Protections (OHRP), and that all approvals are obtained prior to initiating the research at those sites and any stipulations of the board(s) that were required to be addressed prior to the initiation of the research in that country.
- If appropriate, the IRB should ensure that mechanisms are implemented to ensure appropriate management, reduction, or elimination of potential, actual, or perceived conflicts of interest related to all aspects of the research, including financial interests, clinical roles (for example, investigator-patient relationships), and other professional, institutional, or personal roles.
- Level of risk including risk for the conduct of the research at the international site when the research involves living individuals.

5. What should the R&D Committee review and document for international site participation?

- The proposed research is relevant to the VA's mission and the care of Veterans.
- There is scientific merit to the research proposed.
- There are adequate protections for participating human subjects (including privacy and confidentiality), and adequate safety measures for research subjects and personnel engaged in the research.
- The required resources are available and the locations are appropriate where the research will be conducted.
- The research investigator and research team are qualified to conduct the study.
- All appropriate subcommittee approvals have been obtained.

6. What are the requirements for the facility Director memo of approval?

- CRADO approval is not required for a VA investigator to conduct VA research involving international research activities unless it is CSP research. However, the facility Director should approve the conduct of such research before it is initiated. The facility Director should review the minutes of the VA IRB and R&D Committee meeting at which the protocol was approved to ensure that all criteria in item #1 of this guidance were satisfied.
- The memo documents for the record that the facility Director is aware of and approves the request for his/her facility to participate in the proposed international research, and concurs that the part of the research proposed for the international site including the collection of human biological specimen and data derived from human subjects could not be done within the VA or within the United States. The memo should be kept with the R&D file in the Research Office and in the investigator's file.
- If the research proposal is to be submitted for funding through ORD, the facility Director memo may be submitted with other "Just-in-time" documentation.

7. For Cooperative Studies Program (CSP) research.

- For CSP multi-site projects involving international research, review of all required information and approvals will occur during the CSP review process. If the CSP project is approved, the Director, Clinical Science Research & Development (CSR&D) will request the required permission from the CRADO or designee. For CSP Coordinating Center involvement in international research that does not undergo a CSP review process, the CSP Coordinating Center should submit a request to the CRADO through the Deputy Director, CSP. *Note: For CSP studies the memorandum from the facility director of the performance sites is not required.*

REGULATORY AND VHA POLICY REFERENCES:

38 CFR 16, Protections of Human Research Subjects

VHA Handbook 1200.01, Research and Development (R&D) Committee.

VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research.

Federal Register Vol. 70, No. 57 Friday march 25, 2005: Department of Health and Human Services, Protection of Human Subjects, Proposed Criteria for Determinations of Equivalent Protection