

Department of Veterans Affairs
Harry S. Truman Memorial Veterans' Hospital
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Columbia, Missouri

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Issued by: Research

REVIEW OF RESEARCH PROPOSALS

1. **PURPOSE:** To describe the procedures and criteria for the scientific review of research proposals by the Research and Development (R&D) Committee and appropriate subcommittees.
2. **POLICY:** To stimulate a high-quality research program that is responsive to investigators and that maintains compliance with all applicable regulations.
3. **MISSION STATEMENT:** The primary mission of the Veterans Health Administration (VHA) as outlined in M-3, Part I "Research and Development in Medicine," is to provide high-quality medical care to veteran patients. Research serves the VHA mission in three ways:
 - a. Development of new knowledge, new techniques, and/or products that lead to improved prevention, diagnosis, treatment, and control of disease.
 - b. Attraction and retention of the highest quality professional staff that improves care for veterans.
 - c. Cultivation of a stimulating, intellectual environment that is beneficial for both patient care and educational programs.
4. **DEFINITIONS:**
 - a. Human Subjects Research. An activity that either:
 - (1) Meets the Department of Veterans Affairs (VA) and Department of Health and Human Services (DHHS) definition of "research" and involves "human subjects;" or
 - (2) Meets the Food and Drug Administration (FDA) definition of "research" and involves "human subjects."
 - b. Research.
 - (1) DHHS and VA regulations define research as a systematic investigation, including research, development, testing, and evaluation, designed to develop or contribute to generalized knowledge (38 CFR 16.102 [d]). VHA 1200.5 also describes research as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question [Paragraph 3(v)]. Research results do not have to be published or presented at a professional meeting to qualify the experiment or data gathering as research. The intent to contribute to "generalized (scholarly) knowledge" makes an experiment or data collection research, regardless of publication. Research that

is never published is still research. Participants in research studies deserve protection whether or not the research is published.

(2) Under FDA regulations, activities are considered “research” when they involve use of a drug, other than the use of an approved drug, in the course of medical practice; use of a medical device, other than the use of an approved medical device, in the course of medical practice; or involve gathering data that will be submitted to, or held for inspection, by the FDA in support of an FDA-marketing permit for a food, including a dietary supplement that bears a nutrient content claim or a health claim, an infant formula, a food or color additive, a drug for human use, a medical device for human use, a biological product for human use, or an electronic product.

c. Systematic Investigation includes, but is not limited to the following:

- (1) Surveys and questionnaires,
- (2) Interviews and focus groups,
- (3) Analyses of existing data or biological specimens,
- (4) Epidemiological studies,
- (5) Evaluations of social or educational programs,
- (6) Cognitive and perceptual experiments,
- (7) Medical chart review.

d. Human Subjects.

(1) Human Subjects are defined by VA regulations at 38 CFR 16.102(f) and DHHS regulations at 45 CFR 46.102(f) as a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

(a) Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

(b) Interaction includes communication or interpersonal contact between the investigator and subject.

(c) Private Information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may be readily ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(2) FDA regulations define a subject as a participant in research either as the recipient of a test article or as a control [21 CFR 50.3(g), 21 CFR 56.103(3), 21 CFR

312.3(b)]. If the research involves a medical device, individuals are considered “human subjects” when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control [21 CFR 813.3(p)].

(3) Activities are human subject research and subject to VA regulations when (a) they meet the definition of “human subjects research” and (b) meet any of the following criteria:

(a) Any research involving human subjects that is performed at a VA facility,

(b) Any research involving VA patients that is performed at an outside facility, domestic or foreign, including studies with other government agencies or academic institutions,

(c) Any research involving human subjects (in any location) that is conducted by a VA investigator,

(d) All studies that have Institutional Review Board (IRB) approval from other organizations, including approval from other government entities.

(4) A human subject may be either a healthy human or a patient; and may be veterans or non-veterans. Non-veteran subjects may be recruited to participate in VA clinical research projects when there are an insufficient number of veteran subjects available to perform the research adequately or when the design of the project requires a population of subjects with characteristics not present in the veteran population.

e. Clinical Research refers to a clinical investigation. Clinical research is any experiment that involves a test article, one or more human subjects, and that either is subject to requirements for prior submission to the FDA, or is not subject to requirements for prior submission to the FDA under these sections of the Federal Food, Drug and Cosmetic (FD&C) Act, but the results of which are intended to be submitted later to, or held for inspection by the FDA as part of an application for a research or marketing permit. Examples of clinical investigation include: (a) investigational drug clinical trials, (b) medical treatment with investigational devices studies, and (c) medical outcomes studies comparing approved drugs and/or devices.

f. Test Article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug and Cosmetic Act.

g. Biomedical Research refers to research that does not directly involve humans or animals, but may use tissues, cells, blood, or bone from both.

h. Animal Research refers to research that may use live vertebrate animals or tissues, cells, and/or blood samples from an animal within a research project.

i. Principal Investigator (PI) refers to the individual who is accountable for the proposal, performance, and culmination of a research or development project.

j. Co-Principal Investigators (Co-PI) refers to two or more principal investigators who share equally in the accountability for a project.

k. Applicant refers to the person who submits a research proposal for review and who assumes primary responsibility for the conduct of the research. Responsibility includes accountability for the actions of other team members and full compliance with applicable regulations involving human research, animal research, and biosafety. The applicant must be either the PI for local projects or the On-Site Investigator for multi-center and sponsored projects.

5. **PROCEDURES:** Requests for approval to conduct research require the following:

a. All human and biomedical research must be reviewed by the R&D Committee and all applicable subcommittees; all human research will be reviewed by the University of Missouri-Columbia Health Sciences Institutional Review Board (HS-IRB). In some cases, human research may prove to be exempt from applicable federal, state and local regulations. However, "exempt" status will be determined by the HS-IRB, not by the investigator.

b. Investigators will receive assistance, as needed, from the Human Research Compliance Officer (HRCO) in determining whether an activity is human subjects research. Individuals with questions about whether an activity is human subjects research will submit a description of the activity in writing to the HRCO, who will complete a checklist entitled "Determining Whether an Activity is Human Subjects Research" (Attachment 1). The HRCO will provide a written determination to the requestor. If the activity is human subjects research, the requestor will be told that HS-IRB approval will be required. If not, the requestor will be told that the activity is not human subjects research, but that any changes to the activity that may alter the determination will need to be submitted to the HRCO for subsequent review.

c. Research team members who will access VA patients, data, and/or VA space for research purposes are required to have either a VA paid or Without Compensation (WOC) status. To obtain WOC applications, contact the Research Secretary at 814-6550.

d. Obtain and complete a "Request to Conduct Research" application, which can be obtained from the Research Secretary. All research personnel must complete required training prior to review of the application.

e. Submit one copy of the completed application to the Research Secretary in Room B044. Applicants should allow 48 hours for administrative review and notification of any additional materials that may be needed prior to review by the R&D Committee. Prior to submission, the applicant will be responsible for providing documentation of all required training and for initiating all staff appointments required to conduct the study.

f. The complete application package must be received no later than four weeks prior to the next R&D Committee meeting. The R&D Committee meets on the third Wednesday of each month.

g. Applicable subcommittees (e.g., HS-IRB, Research Safety) will conduct reviews and make recommendations prior to the R&D Committee meeting. In the case of the HS-IRB, the results of protocol reviews by the HS-IRB will be communicated to both the investigator and the VA Research Office via VA Form 10-1223. The VA Research Office will transmit HS-IRB actions (i.e., copy of VA Form 10-1223) to the R&D Committee for review. Following approval by the VA R&D Committee, when an investigational new drug (IND) or investigational device exemption (IDE) is involved, VA Form 10-1223 also must be transmitted by the investigator to the Pharmacy Service.

h. A Memorandum of Understanding (MOU) is maintained between the HSTMVH and the University of Missouri-Columbia for the use of the HS-IRB for VA protocols. Therefore, applicants proposing human research studies must submit a separate application to the Health Sciences IRB. The policy of the HSTMVH is to require strict adherence to all Health Sciences IRB-related policies. These policies are located on the HS-IRB website <https://irb.missouri.edu/>.

i. The R&D Committee will carefully review research applications following the required review and approval by other applicable committees such as the Subcommittee for Research Safety (SRS), the Radiation Safety Committee, and the HS-IRB. The R&D Committee will be responsible for ensuring scientific validity, adequacy of design, adequacy of resources, appropriateness from an ethical standpoint, and compliance with applicable policies, regulations, and laws (both state and federal) as related to each research application. In any situation where uncertainty arises regarding applicable policies, regulations, or laws, the R&D Committee and/or HS-IRB will be obligated to obtain outside consultation. The VA Offices of Regional or General Counsel will be consulted if a legal opinion regarding either state or federal laws is needed in relation to the VA research program. When requested by either the R&D Committee or the HS-IRB, the Associate Chief of Staff for Research and Development (ACOS/R&D) will request legal assistance from the Hospital Director, who will transmit the request to the appropriate VA counsel. Final approval of research applications will not occur until policy, regulatory, and/or legal issues are fully resolved.

j. The R&D Committee will carefully monitor research applications that involve INDs or IDEs in order to ensure that the Principal Investigator (if assuming the sponsor function) and/or other sponsoring organizations provide sufficient information (and give attestation) to assure knowledge of the regulatory requirements that govern sponsored research using INDs or IDEs. Information regarding INDs and IDEs will be obtained in the course of the HS-IRB application (which is a component of the Application to Research and Development Committee) and provides additional information to judge the adequacy of the knowledge of the sponsor regarding policies and regulations. At the discretion of the R&D Committee, additional information regarding sponsor knowledge of applicable regulations and policies of the Food and Drug Administration (FDA) will be solicited prior to protocol approval. In addition, if the investigator plans to serve as the sponsor, the R&D Committee will require the investigator to utilize one or more outside auditors (approved by the R&D Committee) to evaluate whether policies and procedures are in place to fully comply with FDA sponsor requirements.

k. Special precautions are required in the review of research applications in situations where state and federal laws may be in conflict. The VA Offices of Regional or General Counsel will consider potentially conflicting issues and offer a legal opinion. In general, federal law is followed unless state law is more restrictive. Other general guidelines are that the VA definition of legally authorized representative is accepted; guardianship issues are determined by state law; procedures for protection of children are determined by state law; privacy matters are determined by VA policy; and state laws are followed where federal laws and regulations do not exist, such as in the case of genetic testing, genetic information, or reporting of child, elder, or spousal abuse.

l. The R&D Committee will either Approve, Disapprove, or Table an application. The applicant will be notified within one week of the R&D Committee meeting of the decision of the Committee and any further required actions. The applicant will be responsible for promptly addressing any concerns identified by the R&D Committee.

6. **MEMORANDUM OF UNDERSTANDING:** For some research applications, a Memorandum of Understanding (MOU) will be required as part of the application process. The applicant will be notified of this requirement during the administrative review of the application. This MOU will be coordinated through the Administrative Officer for Research and Development (AO/R&D) when needed. An MOU may be needed in the following instances:

- a. To secure an application fee for sponsored clinical research.
- b. To secure reimbursement for animal husbandry costs.
- c. To secure reimbursement for staff salary (UMC or VA).
- d. To secure reimbursement for facility use.

7. **DOCUMENTATION:** Complete documentation of the application process, communication with the investigators, and R&D Committee actions (including subcommittees) will be maintained in the Research Office.

a. All applicants will receive notification of R&D Committee actions via email and letter.

b. The HS-IRB will receive, via email, R&D Committee decisions regarding all human research projects.

c. Applicants will annually update a project abstract and will be responsible for obtaining subcommittee approval for all necessary project amendments, adverse events, serious adverse events, or personnel changes.

d. The R&D Committee will annually review the project and maintain close oversight of all VA-approved research studies, including research that is deemed "Exempt" by the HS-IRB, in order to ensure ongoing compliance with ethical standards and/or to manage unanticipated adverse consequences. However, in any situation in which a protocol is terminated prior to the recurring annual review, the Principal Investigator will be required to provide notification to the HS-IRB and the R&D Committee. In the case of protocols involving INDs or IDEs, notification of termination also will be promptly made to the Chief, Pharmacy Service.

e. The ACOS/R&D will report the actions of the R&D Committee to the Chief of Staff, the Associate Director, and the Hospital Director. The R&D meeting minutes will be signed by the Chief of Staff and Hospital Director.

8. **REVIEW OF RESEARCH POLICIES AND PROCEDURES:**

a. In order to make certain that review processes are conducted in a compliant manner, all Research policies and procedures will be reviewed, revised as needed, and submitted to the R&D Committee on an annual basis for discussion and approval.

b. On an annual basis, the HRCO will review the policies and procedures of the HS-IRB to ensure consistency and clarity with regard to VA policies and guidelines; discrepancies will be promptly resolved.

9. **INDEPENDENCE OF REVIEW PROCESS:**

a. In the context of compliance with policies, regulations, and laws, independence of the R&D Committee will be maintained without inappropriate outside influence, with the exception that the R&D Committee may not approve research activities that have been disapproved by other independent committees such as the HS-IRB, the Subcommittee for Animal Studies, the Subcommittee for Research Safety, or the Radiation Safety Committee.

b. Likewise, the independence of the HS-IRB will be maintained, and decisions made by the HS-IRB will serve as the final disposition for the human research components of VA research applications. No other institutional representative, committee, or governing body will have the authority to approve any research activities that have been disapproved by the HS-IRB.

c. Any attempt to exert outside influence on the decision-making authority of research review committees will be promptly reported to the ACOS/R&D and/or the Hospital Director. If a conflict exists with either or both of these institutional representatives, the HS-IRB Administrator or the VA Office of Research Oversight will be immediately notified by any individual who becomes aware of outside influence.

10. **REFERENCES:**

- a. M-3, Part I
- b. VHA Handbook 1200

11. **RESCISSION:** HPM 543-042, dated April 20, 2006

APPROVED:

MARIE L. WELDON, FACHE
Acting Director

Key Words: Research
FDA
DHHS
HRPP

Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions	
	PROTOCOL NUMBER: _____
	PERSON REQUESTING DETERMINATION: _____
	TITLE OF STUDY: _____
KEY:	<div style="border: 1px solid black; padding: 2px; display: inline-block; margin-right: 20px;"> Solid box: All items in the box must be true </div> <div style="border: 1px dotted black; padding: 2px; display: inline-block;"> Dotted box: One item in the box must be true </div>
<input type="checkbox"/> Activity is "Human Research" According to DHHS regulations (All of the following are true)¹	
<input type="checkbox"/> The activity involves research because all of the following are true:	
<div style="border: 1px solid black; padding: 5px;"> <input type="checkbox"/> The activity is a systematic investigation, including research development, testing and evaluation <input type="checkbox"/> Either of the following is true: <div style="border: 1px dotted black; padding: 5px; margin-left: 20px;"> <input type="checkbox"/> The activity is designed to develop generalizable knowledge. <input type="checkbox"/> The activity is designed to contribute to generalizable knowledge. </div> </div>	
<input type="checkbox"/> The activity involves human participants because both of the following are true:	
<div style="border: 1px solid black; padding: 5px;"> <input type="checkbox"/> The data the investigator is planning to obtain are about living individuals <input type="checkbox"/> Either or both of the following is true <div style="border: 1px dotted black; padding: 5px; margin-left: 20px;"> <input type="checkbox"/> The investigator plans to obtain the data through one or more of the following: <div style="border: 1px dotted black; padding: 5px; margin-left: 20px;"> <input type="checkbox"/> Physical procedures performed on those individuals <input type="checkbox"/> Manipulation of those individuals <input type="checkbox"/> Manipulation of those individuals' environments <input type="checkbox"/> Communication with those individuals <input type="checkbox"/> Interpersonal contact with those individuals </div> <input type="checkbox"/> The information to be obtained is both: <div style="border: 1px solid black; padding: 5px; margin-left: 20px;"> <input type="checkbox"/> Private, because either of the following is true <div style="border: 1px dotted black; padding: 5px; margin-left: 20px;"> <input type="checkbox"/> The information is about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place <input type="checkbox"/> The individual has provided the information for specific purposes and can reasonably expect that the information will not be made public (for example, a medical record) </div> <input type="checkbox"/> Individually identifiable, because either of the following is true: <div style="border: 1px dotted black; padding: 5px; margin-left: 20px;"> <input type="checkbox"/> The identity of the participant is or may readily be ascertained by the investigator <input type="checkbox"/> The identity of the participant is or may readily be associated with the information </div> </div> </div> </div>	

Activity is “Human Research” According to FDA regulations (Any of the following are true)

The activity involves an FDA regulated test article because one or more of the following is true:

The activity involves the use of a drug, other than the use of an marketed drug in the course of medical practice:

The activity will involve the use of a drug, meaning one of the following:

- An article recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them
- An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals
- An article (other than food) intended to affect the structure or any function of the body of humans or other animals
- An article intended for use as a component of any article specified in the above items

Either of the following is true:

- The drug is **NOT** approved by the FDA for marketing
- The drug is **NOT** being used in the course of medical practice

The activity involves the use of a medical device, other than the use of an marketed medical device in the course of medical practice:

The activity will involve the use of a medical device, meaning one of the following:

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals
- Intended to affect the structure or any function of the body of humans or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of humans or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes

Either of the following is true:

- The research is testing the medical device for safety.
- The research is testing the medical device for efficacy.

The activity is otherwise subject to FDA regulation:

Data from the activity will be submitted to, or held for inspection by, the FDA.

The activity involves an FDA-regulated article one or more of the following:

- | | |
|---|--|
| <input type="checkbox"/> Food or dietary supplement that bears a nutrient content or a health claim | <input type="checkbox"/> Infant formula |
| <input type="checkbox"/> Food or color additive for human consumption | <input type="checkbox"/> Biological product for human use |
| | <input type="checkbox"/> Electronic product for human use |
| | <input type="checkbox"/> Other article subject to the FD&C Act |

The activity involves human participants because one or more of following is true:

- The test article will be used on one or more humans
- All of the following are true:

- The test article is a medical device
- The medical device will be used on human specimens
- The activity is being done to determine the safety or effectiveness of the device
- Data from the activity will be submitted to, or held for inspection by, the FDA.

- Determined to be human research (Meets either definition)
- Determined to **NOT** be human research (Meets neither definition)

Signed _____

Dated _____