

**Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP)
Human Research Protections Regulatory Requirements**

ORP Human Research Protection Office (HRPO)

1. Department of Defense (DoD) Human Subjects Protection Regulatory Requirements

a. DoD regulations require that the DoD include specific language in contracts or other comparable agreements (e.g., grants, assistance agreements, and cooperative research and development agreements) that might include research involving human subjects. This language identifies the awardee requirements and responsibilities, and requires that any research involving human subjects supported by the award be approved by a DoD Human Research Protection Official (DHRPO) prior to implementation of the research.

b. The awardee is responsible for overseeing execution of the research and must include similar language in subcontracts that support research involving human subjects. In addition, this language:

(1) Allows DoD representatives to independently review and inspect the awardee's research. This may include access to identifiable information or protected health information (thus, subjects must be informed);

(2) Allows DoD representatives to prohibit research that is determined to present unacceptable hazards or is non-compliant with DoD regulatory requirements;

(3) Applies to all human subjects research, whether or not it is determined to be exempt from the regulations.

c. The DHRPO must perform an administrative review of the research before the activities that involve human subjects can begin (e.g., human subject recruitment and data collection). At a minimum, the DHRPO must:

(1) Concur with the extramural institution regarding activities they have determined to be either (a) research not involving human subjects; or (b) research involving human subjects that is exempt from the regulatory provisions of 32 CFR 219.

(2) Confirm the institution has a Federal assurance appropriate for the conduct of the non-exempt research involving human subjects in question. If DoD institutions are engaged in the extramural research, they must have a DoD Assurance.

(3) Review the research protocol for compliance with DoD Instruction (DoDI) 3216.02 "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," accept the IRB determination of level of risk, ensure that the study is compliant with applicable DoD regulatory requirements and approve the

protocol prior to implementation.

(4) Review and accept IRB-approved substantive changes to an approved research protocol before they are implemented.

(5) Ensure the IRB conducts an appropriate continuing review at least annually.

(6) When the research involving human subjects is being conducted in a foreign country, confirm all applicable national laws and requirements of the foreign country have been met and confirm the IRB considered the cultural sensitivities in the setting where the research will take place.

d. The USAMRMC ORP HRPO has designated approval authorities to meet the DHRPO approval requirement for DoD supported research.

2. Requirements for Approval of Extramural Human Subjects Research

a. **Federal Assurance of Compliance.** Each institution engaged in non-exempt human subjects research must have a current Department of Health and Human Services Office for Human Research Protection (OHRP) FWA or DoD Assurance. An IRB review by one of the IRBs listed on the institution's assurance or identified in an Institutional Agreement for IRB Review must be provided. To avoid delays in the HRPO approval process, verify that the institutions engaged in the research have active assurances. The Institution's IRB office or the HRPO can assist in determining if engaged institutions have active assurances and obtaining an assurance is required.

b. **Investigator Qualifications.** A CV or Biosketch of the Principal Investigator (PI) must be provided to the HRPO. Documentation of human subjects protection training (per local policy) for the Principal Investigator and all Associate Investigators (AIs) must be provided to the HRPO prior to approval. A description of roles and responsibilities of study personnel will be requested during the review process to assist in determination of which institutions are engaged in the research.

c. **When applicable, the following DoD unique requirements must be addressed prior to approval:**

(1) 10 United States Code 980. The requirements of Title 10 United States Code 980, which are applicable to DoD sponsored research, must be considered. 10 USC 980 requires that "Funds appropriated to the Department of Defense may not be used for research involving a human being as an *experimental subject* unless- (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

Note that the definition of *experimental subject* is found in DoDI 3216.02 and has a much narrower definition than human subject. Research with experimental subjects must involve an intervention or interaction where the primary purpose of the research is to collect data regarding the effects of the intervention or interaction.

An individual not legally competent to provide informed consent (e.g., incapacitated individuals, cognitively impaired, minors) may not be enrolled as an ***experimental subject*** in a DoD-supported experiment unless participation in the research is intended to benefit each subject enrolled in the study, to include subjects enrolled in study placebo arms. Studies designed in a manner that permits all subjects to potentially benefit directly from medical treatment or enhanced surveillance beyond the standard of care can meet the 10 USC 980 requirements.



10 USC 980 is only applicable to certain intervention studies. It does not apply to retrospective studies, observational studies, blood draws, and tissue collections. Contact the HRPO for further clarification regarding applicability of 10 USC 980 to the proposed research project.

(2) Research Monitor. For research determined to be greater than minimal risk, DoDI 3216.02 requires **that the IRB approve, by name, an independent research monitor with expertise consonant with the nature of risk(s) identified within the research protocol**. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.

The research monitor's duties should be based on specific risks or concerns about the research. The research monitor may perform oversight functions and report their observations and findings to the IRB or a designated official. The research monitor may be identified from within or outside the PI's institution.

Research monitor functions may include:

- observing recruitment and enrollment procedures and the consent process for individuals, groups or units,
- overseeing study interventions and interactions,
- reviewing monitoring plans and UPIRTSO reports;
- overseeing data matching, data collection, and analysis

There may be more than one research monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.

At a minimum, the research monitor:

- may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;

- shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

A biographical sketch or CV and human subject's protection training for the research monitor must be provided. There should be no apparent conflict of interest and the monitor cannot be under the supervision of the PI or other investigators or research staff. If the duties of the research monitor could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the research monitor is not an agent of the covered entity), the PI's institution may require the identity and location of the research monitor to be described in the study Health Information Portability and Accountability Act authorization.

(3) Recruitment of Military Personnel. Civilian investigators attempting to access military volunteer pools are advised to seek collaboration with a military investigator who will be familiar with service-specific requirements.

A letter of support from Commanders of military facilities or units in which recruitment will occur or the study will be conducted will be requested by the HRPO. Some military sites may also require that each volunteer seek written permission from their supervisor prior to participation in research studies.

Special consideration must be given to the recruitment process for military personnel. The Chain of Command must not be involved in the recruitment of military personnel and cannot encourage or order Service members to participate in a research study. For greater than minimal risk research, DoDI 3216.02 requires that an ombudsman be employed when conducting group recruitment briefings with Active Duty personnel to ensure that they understand that participation is voluntary. The use of an ombudsman may be recommended in other situations as well, especially when young enlisted service members, who are trained to follow orders, are being recruited. Service members are trained to act as a unit, so peer pressure should also be considered and minimized if possible.

(4) Payment to Federal Employees and Military Personnel. Under 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited to blood donation and may not exceed \$50 per blood draw. They may not receive any other payment or non-monetary compensation for participation in a research study unless they are off duty or on leave during the time they are participating in the protocol.

(5) USAMRMC Required Protocol and Consent Form Language;

The following must appear in the consent form:

- A statement that the DoD or a DoD organization is funding the study.

- A statement that representatives of the DoD are authorized to review research records.
- In the HIPAA Authorization or HIPAA authorization section of the consent form, representatives of the DoD must be listed as one of the parties to whom private health information may be disclosed.
- If the study involves the participation of a research monitor (as defined by DoDI 3216.02), consideration should be given as to whether the research monitor should also be listed in the HIPAA Authorization as one of the parties to whom private health information may be disclosed.

(6) For Development of Medical Products. Product information must be provided with the protocol submission. The HRPO will assess protocols involving medical products for applicability of FDA regulations. Additional documentation may be requested for investigational products. If the FDA, the IRB, or another regulatory office has determined that the protocol does not require an IND or IDE, provide any documentation available related to this determination.

3. USAMRMC ORP HRPO Submission and Administrative Review Process

a. DoD research programs submit proposals selected for funding to the USAMRMC ORP HRPO for human subjects protection regulatory review. A **Proposal Submission Form**, designed to facilitate the protocol review process, is also submitted for review. This submission form contains information that the USAMRMC funding program may need to solicit from the **Proposal PI** before the proposal is submitted to USAMRMC ORP HRPO.

b. Once the proposal and completed **Proposal Submission Form** have been submitted and triaged, a HRPO staff member will contact the Principal Investigator (PI) to provide the HRPO **Protocol Submission Form** and request the Institutional Review Board (IRB) approved protocol (or an estimate of when the protocol will be submitted for review). The PI must complete the information requested on the **Protocol Submission Form**. Any information that is unknown at the time of protocol submission will be obtained during the review process.

c. When the IRB approved protocol and **Protocol Submission Form** are received, the project will be assigned to a Human Subjects Protection Scientist (HSPS). The HSPS will be the main HRPO point of contact for the PI for information regarding initial review and approval of the protocol, in addition to life cycle reporting requirements. The HSPS will review the protocol for compliance with federal, DoD and state or host nation regulatory requirements and assist the PI with addressing any outstanding issues prior to submission for final HRPO approval. If revisions to the protocol or consent form are required to bring the protocol into compliance, the revised documents must be approved by the IRB prior to HRPO approval.

d. For protocols involving multiple research sites and/or multi-institutional collaborations on a single study, the HRPO must review and approve site specific

documentation prior to participation in human research activities. Note: For protocols involving multiple institutions, the review will proceed much faster if a flow chart or map is provided that outlines the protocol and indicates how each institution is involved.

e. If the project involves execution of all or part of the research outside of the United States the HRPO must confirm all applicable host national laws and requirements of the foreign country have been met and confirm the IRB considered cultural sensitivities in the setting where the research will take place. The Principal Investigator must provide adequate information to the HRPO regarding national laws and requirements and the cultural context in which the research will take place. This information can be provided through completion of applicable sections of the HRPO International Research Submission Form, or through inclusion of applicable information in the protocol.

f. Standard reporting requirements to HRPO are outlined at the end of this document. Additional protocol specific reporting requirements may be included in the HRPO approval memorandum.

4. Reporting Requirements and Responsibilities of the Principal Investigator to the USAMRMC ORP HRPO

a. The protocol will not be initiated until written notification of approval of the research project is issued by the HRPO.

b. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.

c. The Principal Investigator must comply with the following minimum reporting requirements. Specific reporting requirements for the protocol will be included in the HRPO Approval Memorandum. Failure to comply could result in suspension of funding.

(1) Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects.

(2) Any changes of the IRB used to review and approve the research will be promptly reported to the USAMRMC ORP HRPO.

(3) All unanticipated problems involving risk to subjects or others must be

promptly reported by telephone (301-619-2165), by email (HRPO@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the Institutional Review Board (IRB), the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) A copy of the continuing review approval notification by the IRB of Record must be submitted to the HRPO as soon as possible after receipt. For greater than minimal risk research, a copy of the continuing review report approved by the IRB must also be provided. Please note that the HRPO also conducts random audits at the time of continuing review. Additional information and documentation may be requested at that time.

(6) The final study report, including any acknowledgement documentation and supporting documents, must be submitted to the HRPO when available.

(7) The knowledge of any pending compliance inspection/visit by the FDA, DHHS Office of Human Research Protections (OHRP), or other government agency concerning this research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements, must be promptly reported to the HRPO.

Please Note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

For questions regarding the HRPO human research protocol review requirements email hrpo@amedd.army.mil or leave a voicemail at 301-619-2165 and a staff member will contact you.