

PARTNERS HUMAN RESEARCH COMMITTEE GUIDANCE DOCUMENT

Human-Subjects Research Supported by the Department of Defense

Human-subjects research that is supported by the Department of Defense (DoD) or one of its components (e.g., Departments of the Army, Air Force, and Navy and Marine Corps) through a contract, grant, cooperative agreement, or other arrangement with BWH, MGH, McLean or FH must comply with DoD Regulations for “Protection of Human Subjects” at 32 CFR 219 and with DoD Directive 3216.2. Other DoD component-specific requirements may also apply depending on the particular study. This guidance is intended to highlight some of the primary issues for investigators to be aware of when conducting DoD-supported research, but is not a substitute for investigators to obtain project-specific information about DoD’s requirements from the applicable DoD human research protection administrator as directed below. Investigators are expected to include information relevant to and address any applicable DoD requirements in their protocol submissions.

When BWH, MGH, McLean or FH receive DoD funding for human-subjects research, the recipient institution, at the request of DoD, will sign a DoD Addendum to its Federalwide Assurance (FWA) attesting that the institution will comply with applicable federal regulations and DoD requirements for protection of human subjects in research.

DoD Definitions

The following definitions apply to human-subjects research supported by the DoD or one of its components:

Research means any systematic investigation, including research, development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Research involving a human being as an experimental subject means an activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction.

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The phrase "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

DoD DIRECTIVE 3216.2 REQUIREMENTS

The DoD and its components have adopted the “Common Rule” Federal policy for protection of human subjects in research. DoD’s implementation of the Common Rule is found at 32 CFR 219. Additional DoD policies and requirements for the protection of human subjects are described in DoD Directive 3216.2. Most of the DoD requirements outlined in DoD Directive 3216.2 are consistent with Partners Human Research Committee (PHRC) policies and procedures. However, DoD has imposed certain restrictions on the use of surrogate consent and waiver of informed consent and additional human subject protections for research involving greater than minimal risk. Investigators should be aware of these and other additional requirements when developing proposals for DoD support. Some of the main additional requirements are described below. Because components of DoD may have additional requirements for human subject protection, investigators should obtain DoD component specific requirements from the applicable DoD human research protection administrator when applying for funding.

1. Scientific Merit

The IRB must consider the scientific merit of the study.

2. Education and Training

DoD may impose additional education and training requirements on investigators beyond those required by Partners. Investigators should contact their DoD human research protection administrator for information about specific education requirements.

3. Additional Protections for Human Subjects

DoD-supported research must meet the additional protections for pregnant women, human fetuses, neonates, prisoners and children in 45 CFR 46, Subparts B, C, and D unless modified by DoD as below:

a. Pregnant Women, Human Fetuses and Neonates as Subjects

When applying Subpart B regarding pregnant women, human fetuses and neonates, the phrase "biomedical knowledge" shall be replaced with "generalizable knowledge." The applicability of Subpart B is limited to research involving pregnant women as human subjects involved in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus or involving a fetus or neonate as human subjects. Research involving human subjects using fetal tissue must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g. When applicable, investigators are required to provide an assessment of risks and potential benefits to pregnant women and fetuses, nonviable neonates and neonates of uncertain viability and children in the Partners eIRB Human Research Application.

b. Prisoners

When applying Subpart C regarding prisoners, BWH, MGH, McLean and FH rely on the Harvard School of Public Health (HSPH) IRB for review of research involving

prisoners. Contact the Partners Human Research Office before submitting research involving prisoners.

When a previously enrolled subject becomes a prisoner and the researcher asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-subject may continue to participate until the convened HSPH IRB can review this request to approve a change in the research protocol and until the institutional official (IO) and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened HSPH IRB can review this request to approve a change in the research protocol.

The convened HSPH IRB will promptly review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened HSPH IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

c. Treatment of Detainees

Research involving a detainee as a human subject is prohibited. This prohibition does not apply to activities covered by investigational new drug or investigational device provision when for the purposes of diagnosis or treatment of a medical condition in a patient. Such treatment may be offered to detainees with the detainees' informed consent when the medical products are investigational and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices.

d. Children as Subjects

When applying Subpart D to children, the exemption 45 CFR 46 101(b)(2) of research involving survey or interview procedures or observation of public behavior does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

e. Military Personnel as Subjects

Investigators should describe the procedures for recruitment of any military personnel in the protocol submission. The recruitment plan should adhere to the following DoD requirements for selection of subjects:

Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and during off-duty employment or other activities. The IRB may require Principal Investigators to confirm commander support for participation of Service members.

Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decision of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research.

Superiors of Service members (e.g., unit officers, senior NCOs and equivalent civilians) in the chain of command must not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as human subjects. When applicable, superiors excluded from these recruitment sessions will be given the opportunity to participate in the research in a separate recruitment session.

For research that involves more than minimal risk to subjects and when recruitment occurs in a group setting, the IRB will appoint an ombudsman. The ombudsman must not be associated in any way to the research and must be present during the recruitment in order to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor.

f. DoD Civilians as Subjects

DoD Civilians must follow their organization's policies regarding the requirement to obtain permission to participation in research involving human subjects. As above, supervisors are prohibited from influencing the decisions of their subordinates regarding participation in research and may not be present at any human subject recruitment sessions or during the consent process. When applicable, supervisors will be afforded the opportunity to participation as human subjects in a separate recruitment session.

4. Informed Consent

No DoD component may support research involving a human being as an experimental subject without requiring the prior informed consent of the subject with certain limited exceptions described below. Investigators should take these restrictions into consideration when describing the consent process in the protocol submission.

a. Legally Authorized Representatives

When the subjects lack capacity, due to age, condition, or other reason, to make a decision regarding consent to participate in the research, prior consent may be provided by a legal representative of the subject if the IRB determines that the research is intended to be beneficial to the individual experimental subject.

b. Waiver of Informed Consent

The requirement for prior informed consent may be waived by DoD officials if all of the following conditions are met:

- The research is necessary to advance the development of a medical product for the Military Services;
- The research may directly benefit the individual experimental subjects; and
- The research is conducted in compliance with all other applicable laws and regulations.

5. Research Monitor

When the research involves more than minimal risk to subjects, an independent medical monitor must be appointed by name. Medical monitors may be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject management and safety. 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.

The duties of the research monitor are determined on the basis of specific risks or concerns about the research. The research monitor may perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and reports of unanticipated problems involving risks to subjects or others; oversee data matching, data collection and analysis) and report their observations and findings to the IRB.

The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside the study about the research. The research monitor has the 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. Research monitors have the responsibility to promptly report their observations and findings to the IRB.

The IRB must approve a written summary of the monitors' duties, authorities and responsibilities in the data and safety monitoring plan. The IRB must communicate with the monitor to confirm these duties, authorities and responsibilities.

The research monitors must have the expertise consonant with the nature of the risks(s) identified within the research protocol and must be independent of the team conducting the research.

6. Research-related Injury

When the research involves more than minimal risk to subjects the institution must make arrangements for emergency treatment and necessary follow-up of any research-related injury. The Partners Research Consent Form templates include the provision of care for

treatment of research-related injuries. Investigators should contact their DoD human research protection administrator about any additional research-related injury requirements and communicate those to the PHRC.

7. Compensation of Military Personnel

Military personnel may not receive dual compensation for participation in research. This includes military personnel with temporary, part-time and intermittent appointments.

- U.S. military personnel may be compensated for research if they participate in the research when not on-duty.
- Federal employees while on-duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
- Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research

8. Multi Site Research and International Research

For multi site research, DoD requires a formal agreement between organizations to specify the roles and responsibilities of each party. The investigator must contact the DoD research protection administrator to determine the specific requirements for agreements or other documentation of cooperative review arrangements for IRB review of multi site research and communicate those to the PHRC. See PHRC policy on Multi Site Collaborative Human-Subjects Research.

When the research is conducted outside the United States or its territories, and the research involves subjects who are not U.S. citizens or DoD personnel, the investigator must obtain permission of the host country and follow PHRC policy and procedures for research conducted outside the United States or its territories. See PHRC policy on Review of Human-Subjects Research Conducted Off-Site.

9. Surveys of DoD Personnel

Surveys of DoD personnel generally must be submitted to DoD for review and approval.

10. Reporting Noncompliance and Research Misconduct

a. Noncompliance

DoD must be notified of any investigations of alleged noncompliance with applicable human subject protection regulations or DoD requirements outlined in Directive 3216.2 arising in DoD-supported research and of any resulting findings. Reports of noncompliance should be coordinated with the Partners Human Research Committee policy on Noncompliance in Human-Subjects Research and reporting requirements on Reporting to Institutional Officials and Regulatory Agencies.

b. Research Misconduct

DoD must be notified of any allegations of research misconduct and misconduct proceedings in DoD-supported research. The requirement to report is consistent with

the Partners Research Integrity Policy to also follow any specific requirements of the funding agency. Reports of allegations of research misconduct and misconduct proceedings should be coordinated with the relevant institutional Research Integrity Officer.

11. Additional Reporting Requirements

The following findings in DoD-supported research must be promptly (no longer than within 30 days) reported to the DoD human research protection officer:

- Significant changes to the research protocol approved by the IRB
- Results of IRB continuing review
- Change of reviewing IRB
- Any unanticipated problems involving risks to participants or others
- Any suspension or termination of IRB approval
- When the organization is notified by any Federal department, agency or national organization that any part of the Partners Human Research Protection Program is under investigation for cause