RESEARCH SUPPORTED BY A DEPARTMENT OF DEFENSE (DOD) COMPONENT

8/3/2021

The following special considerations apply to research involving human subjects supported by a DoD Component through a contract, grant, cooperative agreement, or other arrangement. Research is considered to involve the DoD if it is conducted in collaboration with DoD employees, uses DoD facilities, or will intentionally include DoD personnel as experimental subjects. Any institution engaging in research that involves the DoD must possess a valid Federal Wide Assurance (FWA). For information regarding Duke University Health System's FWA, see the DUHS IRB web site: https://irb.duhs.duke.edu/about-us/federal-wide-assurance.

All non-DoD institutions conducting human subjects research that receive support from the DoD must comply with the terms of their Federal Wide Assurance; DoD Instruction 3216.02; and relevant policies of the cognizant DoD Component.

Department of Defense components include, but may not be limited to:

- Department of Defense
- Navy
- Office of Naval Research
- Naval Academy
- U.S. Naval Observatory
- Army
- U.S. Army Corps of Engineers
- Military Academy (West Point)
- Air Force
- Air Force Academy
- Marines
- Coast Guard
- Uniformed Services University of the Health Sciences
- National Guard
- Missile Defense Agency
- Defense Advanced Research Projects Agency (DARPA)
- Pentagon Force Protection Agency
- Defense Intelligence Agency
- National Geospatial-Intelligence Agency
- National Security Agency
- National War College, National Defense University
- Defense Health Agency
- Defense Acquisition University
- Special Operations Command

If a Duke investigator is asked to obtain a “DoD assurance of compliance” or “DoD Addendum”, please contact the IRB Director of Compliance or IRB Executive Director for assistance.

Department of Defense Education and Training Requirements

DoD requires that investigators complete human research protections training. There might be specific DoD educational requirements or certification required by different DoD components. The CITI training required for all Duke Health researchers, renewable every three years, meets the training requirements for many DoD Components. Investigators are responsible for ensuring that all study team members engaged in the conduct of research complete the required CITI training, in accordance with DUHS policy. The DoD Component may evaluate the institution’s training program to ensure that personnel are qualified to perform the research, based upon the complexity and risk of the research.

The PI is responsible for identifying any additional specific educational or certification requirements of the sponsoring DoD Component, and should discuss any specific additional DoD educational requirements with their DoD human research protection officer/DoD representative. The PI will ensure that study team members complete any additional training or certification required by the DoD Component. If any additional training requirements pertain to the IRB Chairs, Staff and Members, this information should be shared with the IRB, and the IRB will ensure the requirements are met.

Detainees or Prisoners of War

Research involving a detainee or a prisoner of war as a human subject is prohibited. This prohibition does not apply to activities covered by investigational new drug or investigational device provisions of Title 21, CFR, when the purpose is for diagnosis or treatment of a medical condition in a patient. Such treatment may be offered to detainees or prisoners of war with their informed consent when the medical products are subject to Title 21, CFR, and only when the same product may be available to DoD-affiliated personnel consistent with established medical practices. A prisoner of war is any person captured, detained, held, or otherwise under the control of Department of Defense (DoD) personnel (military and civilian, or contractor employee) except DoD personnel held for law enforcement purposes.

Experimental Subject

An experimental subject is a human being involved in an activity for research purposes, where there is an intervention or interaction for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32 CFR 219.102 (f)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject’s environment, or the withholding of an intervention that would otherwise have been undertaken if not for the research purpose.

Informed Consent & Limitations on Waiver of Informed Consent

In general, no DoD Component may conduct or use appropriated funds to support research involving a human being as an experimental subject without the prior informed consent of the subject, unless a waiver of consent is approved by the Head of a DoD Component (see below).

In addition to the basic and required consent disclosures, consent documents must include:

- 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 case of research intended to be beneficial to the subject, if the subject lacks capacity, due to age, condition, or other reason, to make a legally effective decision regarding consent to participate in the research, prior consent may be provided by a legal representative of the subject. The determination that the research is intended to be beneficial to the subject must be made by an Institutional Review Board (IRB). If consent is to be obtained from the experimental subjects' legal representative, the research must intend to benefit the individual subject.

For research involving a human being as an "experimental subject", informed consent must be obtained in advance from the experimental subject or the subject's legal representative (consistent with 32 CFR 219, if the subject cannot consent). For research that involves no more than minimal risk, as defined by 32 CFR 219, an IRB may alter or waive other required elements of informed consent so long as it still preserves informed consent of the subject (i.e., the consent indicates the subject's participation in the research is completely voluntary and includes the requirement that the subject is informed of research risks). The requirement for prospective informed consent may be waived by the DOHRP (DoD Office for Human Research Protections) or its delegate, if the following conditions are met:
(1) The research is to advance the development of a medical product necessary to the DoD.
(2) The research may directly benefit the individual experimental subject.
(3) The research is conducted in compliance with all other applicable laws and regulations.

If the research subject does not meet the definition of "experimental subject," policies and procedures allow the IRB to waive the consent process.

An exception from consent in emergency medicine research (sometimes referred to as planned emergency research) is prohibited unless a waiver is obtained from the Secretary of Defense.

Requirement to Minimize Undue Influence

Additional protections for military research subjects to minimize undue influence must be present. For research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers (NCOs) shall not influence the decisions of their subordinates to participate or not to participate as research subjects.
Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session.

During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsperson not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate. The IRB must appoint an ombudsperson. The ombudsperson: 1.) must not have a conflict of interest with the research or be a part of the research team; 2.) must be present during the recruitment, monitoring that the recruitment and informed consent explain that participation is voluntary and that information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials; and 3.) should be available to address DoD-

affiliated personnel's concerns about participation.

If planning to recruit DoD-affiliated personnel as subjects in DoD-supported research, refer to DoD Instruction 3216.02.

Conflict of Interest

Conflict of interest can be defined as any situation in which financial or personal interests may compromise or present the appearance of compromising an individual's or group's judgment in conducting, reviewing, approving, managing, and supporting research. Investigators, key research personnel, IRB members, and other personnel must disclose all conflicts of interest, including any financial interests for themselves, spouses, and dependent children. No person shall be involved in any review or approval of a protocol when there may be a conflict of interest.

Noncompliance or Research Misconduct

Any determinations of serious or continuing non-compliance of DoD supported research must be promptly reported to the DoD human research protection officer. Records maintained that document compliance or non-compliance with DoD regulations shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

Department of Navy (DoN)-sponsored research has additional requirements. Consult SECNAV Instruction 3900.39E.

Addressing and reporting allegations of research misconduct shall occur. The DoD Components that conduct or support research shall ensure that data and data collection are conducted in an ethical manner. In cases in which data are not collected in an appropriate manner, the DoD Component shall determine if the misconduct was intentional or reckless; was an isolated event or part of a pattern; had significant impact on the research record; or had significant impact on other researchers or institutions. The DoD Component shall initiate and carry through on any actions that are necessary to ensure resolution of misconduct findings.

Before Initiation of Human Subjects Research

Before initiation of the human subjects research, the Duke Investigator must submit to the DoD human research protection officer:

1. Documentation that the DoD-supported human subjects research has been reviewed and approved by an IRB, including scientific merit, amendments, and additional reviews.
2. Documentation of key investigators' human research protection training.
3. IRB-approved protocol documents.
4. Current FWA and IRB registration numbers.
5. If the research has been determined exempt or does not involve human subjects, Investigator must submit institutional documentation of the determination, and include all protocol-related documents.

Also before the research involving human subjects can begin, the DoD Component must conduct an appropriate administrative review of the research involving human subjects. The purpose of the DoD Component's administrative review is to ensure compliance with all applicable regulations and policies, including any applicable laws and requirements and cultural sensitivities of the country, if the research is conducted in a country other than the United States.

If DoD institutions are also engaged in the research themselves, and collaborating with non-DoD institutions (such as Duke), the DoD institution may rely on a collaborating non-DoD institution's IRB if the following conditions are met:

- Each institution engaged in non-exempt human subject research must have a current federal-wide assurance of compliance (FWA).
- The involvement of DoD personnel in the conduct of the research is secondary to that of the non-DoD institution (Duke).

Reporting to the DoD Human Research Protection Officer

The following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:

1. IRB-approved changes to human subjects research that involve changes to key investigators or institutions; decreased benefit or increased risk to subjects in greater than minimal risk research; addition of vulnerable populations, or DoD-affiliated personnel as subjects; or any other significant changes to the research protocol that are approved by the IRB.
2. Transfer of human subjects research oversight to a different IRB.
3. Notification by any federal body, State agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that the non-DoD institution's DoD-supported research is under investigation.
4. Any problems involving risks to subjects or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DoD-supported human subjects research.
5. The results of the IRB's continuing review, if continuing review is required.
6. Change in status when a previously enrolled human subject becomes pregnant, or when the researcher learns that a previously enrolled human subject is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B.
7. Change in status when a previously enrolled human subject becomes a prisoner, or when the researcher learns that a previously enrolled human subject has become a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart C.
8. A DoD-supported study's closure.
9. When the organization (Duke) is notified by any federal department, agency, or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

For DoD-supported human subjects research, the institution will promptly report to the DoD Component Office of Human Research Protections:

- Unanticipated problems involving risks to subjects or others (UPIRTSOs) and any subsequent actions taken based on the findings, within five days of completion of the report.
- Reports of audits of DoD-conducted or DoD-supported human subjects research by another federal or state agency, official governing body of a Native American or Alaskan native tribe, other official entity, or foreign government, within five business days of discovering that such audit reports exist.
- Allegations of serious or continuing noncompliance related to research involving human participants that are substantiated by investigation, and subsequent actions taken based on the findings, within five business days of completion of the report.

- Substantiated allegations related to **classified** human subjects research must be reported immediately (less than five days) to the DOHRP (DoD Office for Human Research Protections).

Research Involving Vulnerable Populations

Research supported by the DoD that involves vulnerable subject populations shall meet the additional protections of 45 CFR 46, Subparts B, C, and D, as applicable.

Pregnant Women, Fetuses or Neonates

The phrase "biomedical knowledge" in Subpart B of 45 CFR 46, is replaced with "generalizable knowledge." The applicability of Subpart B, 45 CFR 46, is limited to research involving pregnant women as subjects involved in human subjects research that is greater than minimal risk, and includes interventions, as defined in 32 CFR 219, or invasive procedures involving: (a) The woman or the fetus; or (b) Fetuses or neonates as human subjects. Human subjects research using fetal tissue must comply with Sections 289g–289g-2 of Title 42, U.S.C. For research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, the IRB must fulfill its duties in accordance with Subpart B of 45 CFR 46, and the Investigator must receive explicit written approval from the DOHRP (DoD Office for Human Research Protections).

Prisoners

Research involving prisoners cannot be reviewed by the expedited procedure. When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.

Research involving prisoners as human subjects must comply with Subpart C of 45 CFR 46, unless stated otherwise in DoD Instruction 3216.02.

In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:

- The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
- The research presents no more than minimal risk.
- The research presents no more than an inconvenience to the subject.

The IRB must demonstrate that it has fulfilled its duties in accordance with Subpart C of 45 CFR 46.

When a previously enrolled human subject becomes a prisoner, and the protocol has not been reviewed and approved by the IRB in accordance with Subpart C of 45 CFR 46, the principal investigator must promptly notify the IRB. For DoD-supported research, the principal investigator must notify the DoD human research protection officer and other federal agencies, if required.

When a subject becomes a prisoner, if 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 IRB can review this request to approve a change in the research protocol and until the institutional official 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 IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, shall promptly re-review the research protocol [with a prisoner representative present] 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 do not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. The DOHRP (DoD Office for Human Research Protections) must concur with the IRB before the participant can continue to participate while a prisoner.

This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as participants.

Children
Research involving children as human subjects must comply with Subpart D of 45 CFR 46.

The exemption for 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.

Additional Protections for Privacy and Confidentiality in Research
A non-DoD institution conducting human subjects research with DoD support may obtain a Certificate of Confidentiality (CoC) pursuant to Section 241 of Title 42, U.S.C. A CoC prohibits disclosing or providing, in any federal, State, or local civil, criminal, administrative, legislative, or other proceeding, or to any other person not connected with the research, the name of any individual or any such information, document, or biospecimen that contains identifiable information about the individual, created or compiled for purposes of research. Exceptions to the CoC must be listed in all informed consent documents, as stated in Section 241 of Title 42, U.S.C.

Research Involving Large-Scale Genomic Data (LSGD)
DoD-supported research involving LSGD collected on DoD-affiliated personnel is subject to additional requirements. The disclosure of DoD-affiliated personnel's genomic data may pose a risk to national security; accordingly, such research requires administrative, technical, and physical safeguards commensurate with risk, including the secondary use or sharing of de-identified data or specimens. All research involving LSGD collected from DoD-affiliated personnel will obtain an HHS Certificate of Confidentiality. Research involving LSGD collected from DoD-affiliated personnel is subject to DoD Component security review to ensure the adequacy of the proposed administrative, technical, and physical safeguards, including the secondary use or sharing of de-identified data or specimens.

Research Monitor

When following DoD requirements, a research monitor is no longer required. Researchers may remove the requirement for a research monitor from existing open DoD-supported studies through an Amendment approved by the IRB.

Additional Requirements for Research Funded by a DoD Component

1.) New research protocols and substantive amendments to approved research must undergo scientific approval prior to or concurrent with IRB review. Substantive amendments are those that involve more than minimal risk and thus require full board review. For non-exempt research, the IRB must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of the scientific merit.

2.) Surveys performed on DoD personnel must be submitted, reviewed, and approved by the DoD after the research protocol is reviewed and approved by the IRB. When a survey crosses DoD Components, additional review by all Components is required.

3.) All human subjects research that is determined to be greater than minimal risk must meet the requirement of 32 CFR 219.116, to provide subjects with an explanation as to whether any compensation and any medical treatments are available for research–related injuries. The IRB will determine whether research involving minimal risk also might include a similar arrangement for research-related injury. DUHS IRB's standard language for research- related injury will be used. Added information may be included if required by the DoD component.

4.) Additional safeguards for research conducted with international populations must be provided. Research involving human subjects who are not U.S. citizens or DoD personnel, conducted outside the United States, its territories and possessions, requires permission of the host country as evidenced by certification from the host country or local ethics review. The local laws, regulations, customs, and practices of the host country will be followed.

5.) Civilian investigators attempting to access military volunteers for research should seek collaboration with a military researcher familiar with service-specific requirements.

6.) Limitations on compensation for US military personnel must exist. Dual compensation must not occur, such that an individual must not receive pay or compensation for research occurring during duty hours. However, US military personnel may be compensated for research if the subject is involved in the research when not on duty.

7.) 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.) Recordkeeping requirements include maintaining adequate documentation of DoD- supported research involving human subjects, and establishing procedures for fulfilling DoD reporting requirements.

9.) All research involving the use of investigational test articles (drugs, devices and biologics) shall comply with U.S. Food and Drug Administration (FDA) regulations. An Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) must be filed with the FDA whenever research involving human subjects is conducted outside the United

States with drugs, devices or biologics, which would require filing of an IND or an IDE if the research were conducted in the United States.

10.) Classified research with human subjects is held to the same ethical principles and human subject protections as unclassified research and must receive prior approval from the Secretary of Defense (SECDEF) (SECDEF Memorandum of December 13, 1999). Classified research is not eligible for review under expedited review procedures. Waivers of consent are prohibited for classified research. Non-exempt classified research must be conducted following the requirements of Instruction 3216.02. DUHS does not ordinarily perform classified research. In the event a request to do so is submitted, and the research is supported or funded by DoD, the DUHS HRPP will follow the requirements of Instruction 3216.02.

11.) For collaborative multi-site research, an appropriate written agreement shall be established between the collaborators that includes a Statement of Work and specific assignment of roles and responsibilities for each party.

12.) Research on chemical and biological weapons is generally not approvable, subject to certain exceptions for prophylactic, protective, or other peaceful research. See 50 U.S.C. 1520a (reference (g)).

13.) When following DoD regulations and requirements, the definition of “minimal risk” based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological 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 focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

Additional Requirements for Department of Navy (DoN) Supported Research

1.) U.S. Navy-wide survey research requires additional review. Surveys, other than those executed entirely within the command, typically require Navy Survey Review and Approval. The Navy Survey Approval Manager may require IRB review of the survey instrument prior to granting approval.

2.) All research involving the use of investigational test articles (drugs, devices and biologics) shall comply with applicable FDA regulations. An Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) must be filed with the FDA whenever research involving human subjects is conducted outside the United States with drugs, devices or biologics, which would require filing of an IND or an IDE if the research were conducted in the United States. The Surgeon General of the Navy (Navy SG), Commanders, and Commanding Officers may serve as sponsors for INDs and IDEs. The Navy SG may consider an IND/IDE equivalency in circumstances where the requirements may not be possible or feasible in international research. Investigators may not be designated as sponsors for INDs and IDEs.

3.) Oversight by the DoN HRPP through headquarters-level review of research protocols (including relevant IRB meeting minutes) after local institutional approval and site visit of the institution's HRPP will occur. This may be delegated to levels of command or authority appropriate to ensure compliance, and include procedures for the investigation and resolution of

allegations of non-compliance, and may include procedures for headquarters-level administrative review of research. A DoD Component may delegate headquarters-level research review responsibility to another DoD Component for purposes of efficiency and consolidation of functional offices.

4.) Recordkeeping requirements include maintaining adequate documentation of DoD-supported research involving human subjects and establishing procedures for fulfilling DoD reporting requirements. Consult SECNAV Instruction 3900.39E for recordkeeping requirements for DoN- supported research.

5.) Reports to the DoN Human Research Protection Program (HRPP) Office and appropriate sponsor(s) must occur for:

(a) All suspensions or terminations of previously approved DoN-supported research protocols;
(b) The initiation and results of investigations of alleged non-compliance with human subject protections;
(c) Unanticipated problems involving risks to subjects or others, or serious adverse events in DoN-supported research;
(d) All audits, investigations, or inspections of DoN-supported research protocols;
(e) All audits, investigations, or inspections of the institution's HRPP conducted by outside entities (e.g., the FDA or OHRP);
(f) Significant communication between institutions conducting research and other federal departments and agencies regarding compliance and oversight;
(g) All restrictions, suspensions, or terminations of institutions' assurances.

References:

1) DoD Instruction 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and Supported Research", issued April 15, 2020

2) Department of Navy, SECNAV Instruction 3900.39E, issued May 29, 2018

3) 50 U.S.C. 1520a

4) 32 CFR 219

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