

AAHRPP DOCUMENT # 86

**UNIVERSITY OF ALABAMA
HUMAN RESEARCH PROTECTION PROGRAM**

GUIDANCE: Department of Defense Regulations for Human Subjects Research
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The purpose of this guidance is to assist investigators to know and comply with Department of Defense (DoD) regulations and procedures (DoD-Directives or DoDD) for conducting human subjects research with members/employees of any unit of the DoD. This guidance reflects the most recent re-issue of DoD regulations completed in November 2011. It applies to all biomedical and social/behavioral research involving human subjects from the DoD and covers all kinds of support agreements (grants, contracts, cooperative agreements, Development Agreements [CRADs] or other arrangements], regardless of the source of the funding, funding appropriation, nature of support, performance site, or security classification. It also applies to human subject research using DoD property, facilities, or assets.

While all units of the DoD abide by the Common Rule, including Subparts B-D (protections for vulnerable populations of pregnant women, prisoners, and children), some components have unique policies and procedures that reflect the characteristics of the agency (e.g. leadership, culture, risk tolerance, mission) for approving institutions and assuring compliance for their sponsored research.

It is the responsibility of the Principal Investigator (PI) to ensure that all additional Department of Defense requirements for human subjects protection are met. It is the responsibility of the University of Alabama IRB to ensure that all additional Department of Defense requirements for human subjects protection have been met before IRB approval is granted. *The UA IRB will follow its standard institutional policies for making decisions about human subjects research for DoD components (whether the study is research, degree of risk, etc.)*

Regulations and directives that specifically address the protection of human subjects in research sponsored by any component of the US Department of Defense (DoD) include DoD Directive 3216.02 (dated November 8, 2011); DoD: Dual Compensation Act, 24 U.S.C.301; Section 980 of title 10, USC; 32 CFR Part 219; DoD Directive 6200.2 (dated August 1, 2000), SECNAVIST 3900.39D, para. 6a(6), and others.

OVERVIEW OF REQUIREMENTS

Identification of DoD-Sponsored Research

When submitting an application for human subjects research to the UA IRB, the PI must identify the research as sponsored or funded by a DoD component (as defined in Department of Defense Directive 3216.02). The PI is responsible for identifying DoD component requirements specified in the grant application guidelines and for advising the IRB staff and IRB of the requirements.

DoD components include, but are not limited to:

- Navy
- Office of Naval Research
- Naval Academy
- US Naval Observatory
- Army
- US Army Corps of Engineers
- Military Academy (West Point)
- Air Force
- Air Force Academy
- Marines
- Coast Guard
- Coast Guard Academy
- 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
- Tricare Health System

Department of Defense Ethics Education Requirements

DoD-approved education and training in human research protections are required for personnel involved in the conduct, review, or approval of research sponsored by a DoD Component. Each DoD Component has educational requirements in the ethical conduct of human subjects research. The type and extent of training depend, in part, upon the duties and responsibilities of the persons involved in the research. Further, research ethics training is incorporated into continuing education for activities of DoD Components that involve the conduct of human subjects research (DoD Directive 3216.02, November 8, 2011). The DoD Component may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

- The PI and research team complete all initial and continuing mandatory education requirements for human subjects protections in accordance with DoD policy.
- The PI is responsible for identifying specific educational or certification requirements of the sponsoring DoD Component and conveying those requirements to the IRB. The PI consults the DoD Component, as appropriate, to identify education requirements.

- ORC staff, with assistance from the PI, determines the need for orientation and/or education of the IRB chair, members, staff, and Institutional Official regarding DoD-specific education requirements.
- IRB staff assists the PI, study personnel, and all IRB personnel, as identified above, in accessing the necessary human subjects training and certifications required for IRB approval.
- The PI, study personnel, and IRB members and staff complete DoD-specific research ethics training, as applicable, and the PI submits documentation of training completion to the IRB and to the DoD Component, as appropriate.
- Office for Sponsored Programs (OSP) staff includes relevant certifications, as appropriate, in the sponsored research agreement.
- The IRB does not approve DoD-supported research until the PI and research team have completed required education and the appropriate certifications are in place.

Research Monitor Required: Greater than Minimal Risk Studies

For DoD-sponsored research involving greater than minimal risk to subjects, the DOD requires appointment of an independent research monitor. The research monitor has the authority to stop a research study in progress; remove individuals from the study; and take any steps to protect the safety and well-being of subjects until the IRB can assess the research monitor's report.

- The IRB is responsible for making the determination that the research is minimal risk or greater than minimal risk.
- The PI identifies a candidate for the position of research monitor, taking into account the nature and disciplinary focus of the study and the likely type of expertise required. The PI attaches to the IRB application a copy of the monitor's curriculum vitae and a letter from the monitor accepting the role.
- The PI conveys to the monitor relevant DoD-specific orientation/education requirements of the role (see also Department of Defense Ethics Education above.)
- The IRB reviews the information regarding the monitor and determines whether the individual designated meets the DoD requirements for educational and professional expertise (see Definitions above). The IRB also ensures that the research monitor is independent of the research team.

Research Involving International Citizen Populations

- The PI provides the necessary information within the application for human subjects research, as appropriate, on the subject populations, the cultural context, and the languages understood by the human subjects. The PI is responsible for identifying local laws, regulations, customs and practices and following them when designing and implementing the research. The PI is responsible for providing information and materials as described in *UA IRB Policy: Review and Oversight of Research Conducted at Multiple Sites* to non-UA-affiliated performance sites. Prior to IRB approval, all applicable national laws and requirements of the foreign country must be met and the IRB must consider the cultural sensitivities in the setting where the research will take place.
- To ensure the IRB has appropriate knowledge of the local context, the IRB may use a consultant in accord with its standard operating procedures outlined in *POLICY: Obtaining Additional Expertise or Expert Consultation for IRB Reviews*.

Additional Safeguards for International Research:

Additional safeguards may be needed for research involving international populations. The IRB will appraise any potential risks (physical, social, economic, psychological, or legal) based on the protocol and subject population (See UA IRB Document # 186: Identifying and Minimizing Risks to Human Research Participants).

The IRB is responsible for implementing additional safeguards, when appropriate, for international research. In these cases, the UA IRB wishes to see evidence in the IRB application that the investigator is aware of these issues, either through personal knowledge and experience working in that country/culture/community or through the presence of a qualified consultant. For example, does the research site require permission of a village headman or chief before one can approach participants? May male interviewers interview or treat female participants without the consent or presence of a related male? What local beliefs or customs will influence response to questions? What does the target group consider to be respectful behavior? How was the nature and appropriateness of any incentives determined? Will participants or their community receive anything that would empower them in some way, other than any direct personal benefits from the research? (See *UA IRB FORM: Checklist for Reviewers and Investigators for examples of what the IRB wishes to see in applications*) The IRB application should identify any cultural/local consultants on the personnel page and describe their efforts and availability.

The IRB will give special attention to potential risks involved with certain international participants that present special issues for their inclusion or exclusion in research or their treatment within a study. This may include, but is not limited to, coercion, undue influence, or stigmatization. Investigators must justify the inclusion or exclusion of such persons from the research and explain how the vulnerable characteristic will be addressed to protect human subjects. IRBs must evaluate the appropriateness of

sample characteristics or size and the adequacy of protection for vulnerable participants.

In reviewing research involving international populations, the IRB will use a reasoned, nuanced approach to evaluating vulnerability and risk protection rather than taking a simple population or “labeled group” approach. The IRB will review study design to determine if it maximizes the safety of the research participants through appropriate data collection, assessment and monitoring. These evaluations will especially consider populations specified by 21 CFR Part 56 and 45 CFR Part 46 as particularly vulnerable to risks inherent in research. The IRB is authorized to approve research under the guidelines provided by 21 CFR Part 56.111 and 45 CFR Part 46.111 – IF:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits;
- Selection of subjects is equitable;
- Informed consent will be sought from each prospective subject;
- Informed consent will be appropriately documented;
- The research plan, where appropriate, makes adequate provision for monitoring data;
- There are adequate provisions to protect the privacy of subjects and the confidentiality of the data.

The IRB may seek consultation to determine that risks to international research populations have been adequately identified and addressed. The UA IRB may also rely on academic institutions abroad for consultation on these matters. The PI and IRB staff will also consult with the sponsoring DoD component, as appropriate.

Investigators shall provide all required or requested information to the IRB for the IRB to make risk determinations. Implementation of this policy will ensure the safety of human subjects participating in international research by applying a formal and rigorous analysis to identify and minimize the risks inherent in research for all populations.

Host-country national approval

For international studies subject to the 45 CFR 46, U.S. regulations require that a study must be reviewed and approved by an IRB in the area where the study will be conducted. It is not sufficient that a U.S.-based IRB approve a study; it must also be approved by a board comprised of members of the community in which the study will be conducted. This requirement is in addition to complying with host country national guidelines or regulations. National systems for the approval of human subjects' research vary widely from country to country. Some countries (e.g., India and The Gambia) have clear and robust guidelines for externally sponsored research as well as

for domestic projects, while other countries do not have review committees responsible for human subjects protection. In such cases, the country may have other means of approving human subjects' research, such as review by the Ministry of Health (MOH).

Verifying Investigator Permission to Conduct International Research

For countries with specific guidelines and regulations involving human subject research, the UA IRB will require documentation of approval from the appropriate entity (e.g., local or university-based ethics, national ministry or department). Receipt of this documentation by the UA IRB is required to verify that the investigator has permission to conduct research in that country.

International Collaborators: When an ethical review board exists at the host institution and meets the U.S. criteria for an IRB, it can be registered and used as the IRB of record for the study. A local independent IRB can also be registered and used as the IRB of record for the study. If an ethical review board does not exist, the U.S. collaborator will need to supply information to the foreign collaborator on the makeup and duties of an IRB and assist in the formation of a suitable IRB. The Office for Human Research Protections (OHRP) publishes an annual list of international regulations from 90+ countries and provides information about a number of regional and international organizations. Go to <http://www.hhs.gov/ohrp/index.html> and click on "international" in the left-hand column.

Provisions for Human Subjects Research Using Investigational Test Articles

Investigators may not be designated as sponsors for drug, device or biologic studies (INDs and IDEs).

Research Involving US Military Personnel as Research Participants

The PI submits the IRB application for human subjects research incorporating additional safeguards to minimize undue influence from individuals within a potential participant's chain of command. The PI should consult the sponsoring DoD Component, as necessary, to assist him in making provisions for these additional safeguards.

- If the research involves greater than minimal risk to participants and involves military personnel, the PI must include in the application a plan to ensure that officers, senior or other non-commissioned officers cannot influence the decision of their subordinates in their recruitment plan, including their presence during the consenting process.
- The PI must also include a plan to provide separate recruitment procedures for officers and senior non-commissioned officers to participate in the research study.

- The PI must have a witness independent of the research team present during the recruitment and consenting process. The IRB will not waive this requirement for DoD sponsored research.
- For DoD-sponsored research that is greater than minimal risk and which involves U.S. military personnel, an independent witness or ombudsman is present when recruitment involves a percentage of a unit.
- The IRB will review any proposed compensation to ensure that it does not violate the Dual Compensation Act which prohibits military personnel from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week.
- DoD policies do not apply when U.S. military personnel incidentally participate as subjects in a study that is not DoD-sponsored or supported and U.S. military personnel are not the intended target population.
- For DoD-sponsored research, non-federal persons may be compensated for their participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

Research Involving Pregnant Women, Prisoners, and Children

Research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C, and D.

- For purposes of applying Subpart B, the phrase "biomedical knowledge" shall be replaced with "generalizable knowledge."
- The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants.
- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
- Research involving prisoners cannot be reviewed by the expedited procedure.
- 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 participant.

- If a participant becomes a prisoner and the investigator asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the organizational 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-participant (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 participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human participant, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant's confinement does 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-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.
 - Research involving a detainee as a human participant is prohibited, except this prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.
- Research involving children cannot be exempt.

The IRB is aware of the definition of "prisoner of war" for the DoD component granting the addendum.

Research Involving Prisoners of War and Detainees

Research involving any person captured, detained, held, or otherwise under the control of DoD personnel is prohibited.

Research Involving Federal Employees and Non-Federal Persons

- 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.

Classified Research

Classified research must receive prior approval from the Secretary of Defense and must undergo a full board review with the following stipulations:

- At least one non-affiliated member must be a non-Federal employee.
- Any IRB member who disagrees with a majority decision to approve a project may appeal the decision to the Secretary of Defense.
- The IRB must determine whether potential human subjects need access to the classified information to make a valid, informed consent decision.

For classified research, waivers of consent are prohibited. Informed consent procedures must include: (a) identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk and (b) a statement that the research is classified and an explanation of the impact of the classification.

Research in Which Legally Authorized Representatives (LARs) Provide Consent

According to military law and DoD Directive, informed consent may be provided by a legally authorized representative of participants if:

- The participant lacks capacity, due to age, condition, or other reason to make a decision regarding consent to participants in the research; and
- The IRB has determined that the research is intended to be beneficial to the individual participant.

See UA Policy: Investigator Responsibility for Informed Consent Process and Documentation” for obtaining consent using LARs and UA Guidance: Alabama Law on Children, Minors, Consent, and Other Research-Related Topics for a definition of “Legally Authorized Representative”.

Waiver of Consent and Exception from Informed Consent in Emergency Medicine

If a research subject meets the definition of “experimental subject,” DoD regulations prohibit a waiver of consent unless the PI obtains a waiver from the Secretary of Defense.

- The IRB makes the determination as to whether the research subject meets the definition of “experimental subject.”

- The IRB shall not approve a waiver of consent if the research subject meets the definition of “experimental subject” unless the Secretary of Defense has issued a waiver.
- The IRB is allowed to waive the consent process if the research participant does not meet the definition of “experimental subject”.

DoD regulations prohibit an exception from informed consent in emergency medicine research unless the PI obtains a waiver from the Secretary of Defense.

- The IRB shall not approve an exception from informed consent in emergency medicine research unless the PI has obtained a waiver from the Secretary of Defense.

Multi-Site or Collaborative Research Requirements

The PI in conjunction with OSP staff should ensure that the formal research agreement between participating institutions includes a statement of work and specifies the roles and responsibilities of each party. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

- When developing a proposal for DoD funding or other support that involves other collaborating institutions, the PI consults the sponsoring DoD Component and the Compliance Officer early in the proposal development process to identify additional requirements for multi-site research.
- In order to ensure consistent protection of subjects under DoD requirements, a PI conducting DoD-sponsored multi-site research submits information to the IRB about how information about protection of human subjects will be communicated to, implemented, and monitored at sites that are and are not affiliated with UA. See POLICY: Review and Oversight of Research Conducted at Multiple Sites.

Provisions for Research-related Injury

The PI is responsible for informing IRB staff of the DoD Component’s requirements for the provision of care in the case of a research-related injury. If the DoD Component has stricter requirements than the Common Rule or UA, the PI and OSP should ensure this language is included in the research agreement, and the IRB staff will verify the language is consistent with the language in the consent document.

Additional DoD Review Required Prior to Study Initiation

Once the IRB completes its review and issues approval, the PI submits documentation of IRB approval, the risk level, and the expiration date of the research to the DoD Component sponsoring or supporting the study.

- The PI may not initiate the study until the human research protection officer (HRPO) within the sponsoring DoD Component reviews and approves the IRB approval and other submitted documentation.
- The DoD may also request additional documentation to verify compliance with federal and DoD policies, including minutes related to the research. As appropriate, IRB staff provides the PI any additional information pertinent to IRB review, which may not be under a PI's purview (e.g., IRB minutes). The PI sends requested information to the DoD.
- If the study is for DoD-sponsored survey research or survey research within the DoD that involves DoD personnel, either military or civilian, the PI and the IRB identify any requirements for an additional level of DoD review of the study. Surveys typically require DoD Survey Review and approval. The PI submits surveys and all required documentation relevant to survey research review to the requesting DoD Component.
- The PI notifies OSP and IRB staff upon receipt of relevant HRPO authorization and/or DoD Survey Review approval, as appropriate. OSP staff establishes the account only after receiving certification of final human subjects and survey review and approval from the HRPO or relevant DoD designee.

Scientific Review for Substantive Amendments of Approved Protocols: Prior Scientific Review Required

DoD requires that all substantive amendments to approved DoD research involving human subjects receive scientific review prior to IRB review. Therefore, the Department Chair (or designee) needs to complete departmental scientific review and approval (e.g., FORM: Signature Assurance Sheet) for submission by the investigator with the Project Review/Amendment Form to the IRB for review.

Non-compliance Reporting Requirements

UA will report to DoD any of the following for DoD-related research:

- Suspension or Termination of the research;
- IRB approval of significant changes to the research protocol;
- Results of IRB continuing review;
- Change in reviewing IRB;
- Any Federal department or agency or national organization for cause investigation involving a DoD-supported human research protocol;
- Initiation and results of investigations of alleged non-compliance;

- Unanticipated problems involving risks to subjects or others, and/or serious adverse events
- Any audit, investigation or inspection of DoD-supported research;
- Any audit, investigation or inspection of the institution's HRPP conducted by outside government entities (e.g., FDA or OHRP);
- Significant communication between institutions conducting research and other federal departments and agencies regarding compliance and oversight;
- Any restriction, suspension or termination of the institutions' assurance.
- *See UA Policies: Reportable Events, Unanticipated Problems, and Adverse Events Involving Risks to Participants and Others; Monitoring of Previously Approved Protocols for Cause: Suspension and Termination; Allegations and Finding of noncompliance for details of what is reportable or noncompliant and the procedures for reporting to Institutional Officials and Regulatory Agencies.*
- All findings of serious non-compliance shall be reported to the DoD, Director, Defense Research and Engineering.
 - Determinations of serious or continuing non-compliance of DoD-supported research must be promptly (no longer than within 30 days) reported to the DoD human research protection officer.

Research Misconduct

For DoD-funded activities in which an inquiry identifies sufficient evidence to proceed to an investigation, UA will notify the official specified in the applicable award. Following completion of the investigation, UA will provide a copy of the evidentiary record, the report of the investigation, recommendations made to the institution's adjudicating official, and the written response of the individual that is the subject of the allegation to any recommendations. This information will be provided to the Contracting Officer, Grants Officer, Agreement Officer, or other designated official. See UA Policy: Guidance: General Responsibilities of Investigators Policy Concerning the Maintenance of High Ethical Standards in Research and Other Scholarly Activities).

Maintenance of Records

IRB staff maintains IRB records for DoD-sponsored research in accordance with its policy: Maintaining IRB Records. The PI may also be required to maintain additional research-related and compliance documents in his files. The PI is responsible for fulfilling these requirements and should contact the DoD Component to determine their specific requirements.

REFERENCES

Department of Defense Directive, DoD 3216.02, November 8, 2011, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research" (<http://www.dtic.mil/whs/directives/corres/pdf/321602p.pdf>)

Title 24 United States Code Section 30 Dual Compensation Act, 24 U.S.C. 30.

Title 10 United States Code Section 980

SECNAVINST 3900.39D - "Human Research Protection Program"

DoD Directive 6200.2 – "Use of Investigational New Drugs for Force Health Protection"

DoD Directive 3210.7 – "Research Integrity and Misconduct"

32 CFR 219 (National Defense regulations)

45 CFR 46, Subparts B, C, and D (HHS regulations)

21 CFR 50, 56, 312, 812, 600 (FDA regulations)

42 CFR 93 (PHS regulations)