

DON HRPP HANDBOOK
16 May 2015

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SENSITIVE

**DEPARTMENT OF THE NAVY
HUMAN RESEARCH PROTECTION PROGRAM
(DON HRPP)
HANDBOOK**



**This handbook is for guidance only.
Do not cite this document as a requirement.**

FOREWORD

1. This handbook is approved for use by the Department of the Navy (DON) and intended to assist Human Research Protection Programs at DON commands in understanding their responsibilities associated with research conducted or supported by the DON.
2. This handbook provides guidance to facilitate compliance with ethical principles, laws, regulations, and policies for the protection of human research subjects.
3. Comments, suggestions, or questions regarding this document should be e-mailed to usn.ncr.bumedfchva.mbx.DON-HRPP@mail.mil with “DON HRPP HANDBOOK FEEDBACK” as the subject line.

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HANDBOOK**

1. SCOPE

1.1 Scope. This handbook provides guidance to facilitate compliance with ethical principles, laws, regulations, and policies for the protection of human subjects. This handbook is for guidance only and cannot be cited as a requirement. Local HRPP and IRB policies and procedures may be more restrictive.

2. APPLICABLE DOCUMENTS

2.1 General. The documents listed below are not necessarily all of the documents referenced herein, but are those needed to understand the information provided by this handbook.

2.2 Government documents

2.2.1 Specifications, standards, and handbooks

Department of Defense Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research

Secretary of the Navy Instruction 3900.39D, Human Research Protection Program

2.2.2 Other Government documents, drawings, and publications

United States Code, Title 10, Subtitle A, Part II, Chapter 49, Section 980, Limitation on Use of Humans as Experimental Subjects

Code of Federal Regulations

Title 21, Part 50 - Protection of Human Subjects

Title 21, Part 56 - Institutional Review Boards

Title 32, Part 219 - Protection of Human Subjects

Title 45, Part 46 - Protection of Human Subjects

Title 48, Part 252 – Defense Federal Acquisition Regulation Supplement

Federal Register

Title 63, Federal Register 60364–60367 of 9 Nov 98

Federal Guidance

FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees; March 2006

FDA Information Sheets: Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection; January 2009

3. RESERVED

4. GENERAL GUIDANCE

4.1 Human subject research determination. See Table I.

4.1.1 Policies and procedures. The DON command should have policies and procedures for determining whether an activity is research involving human subjects. The definition (32 CFR 219.102 and DoD Instruction 3216.02, Glossary Part II) should be provided to Institutional Officials, researchers, and IRB staffs. The process should include:

a. Identification of the entity or office that can provide a determination, e.g., IRB Chair, IRB Vice Chairs, designated IRB administrators, or designated officials of the HRPP. Investigators shall not make this determination [SECNAVINST 3900.39D, paragraph 4a(3)].

b. Criteria used to make determinations; and

c. Steps to be taken to inform individuals whether an activity is research involving human subjects.

4.1.2 DoD-DON Assurance. A DoD-DON assurance, which is originated by the command engaged in human subject research, states that the command will comply with federal, DoD, and DON requirements for human subject protections. The DoD-DON assurance is reviewed and approved by the Surgeon General of the Navy [SECNAVINST 3900.39D, paragraph 6a(4)(b)]. The assurance requirements apply to all programs within the DON command and are not restricted by funding source (intramural or extramural), funding appropriation, nature of support, program budget activity, program title, or security classification. In summary, all researchers conducting research involving human subjects must be covered either directly under their command's Federal assurance or indirectly using an Individual Investigator Agreement (IIA) [DoD Instruction 3216.02, enclosure 3, section 2, subparagraph 2a(2)(a)].

TABLE I. HUMAN SUBJECT RESEARCH DETERMINATIONS

(1) Does the activity meet the definition of research as defined in 32 CFR 219?

Answers to all the questions below must be “YES” to meet the definition of research

- (a) Is the activity an investigation?
- (b) Is the investigation systematic?
- (c) Is the systematic investigation designed to develop or contribute to knowledge?
- (d) Is the knowledge generalizable?

(2) Do the subjects meet the definition of Human Subject under 32 CFR 219?

Answers to all the questions below must be “YES” to meet the definition of human subject

- (a) Is the investigator conducting the Research gathering data about living individuals?
[32 CFR 219.102(f)]
- (b) Will the investigator gather data through either of the following mechanisms:
Physical procedures or manipulations of those individuals or their environment
 (“intervention”) or communication or interpersonal contact with the individuals
 (“interaction”)?

OR

- (c) Will the investigator gather identifiable (identity readily ascertained by the investigator or associated with the information) data that is either:
 - Data about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or
 - Data provided by or from individuals for specific purposes in which the individuals can reasonably expect that it will **NOT** be made public, such as a medical record (i.e., “Private information”)?) [32 CFR.102 (f)(2)]

(3) Does the research meet the definition of “Research Involving Human Subjects” under DoD Instruction 3216.02, Glossary Part II.:

Meets the definition of human subject research as defined above at 32 CFR 219.102(f); and
answers to the following questions must be “No”

- (a) Is the activity carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease in Service members and other mission essential personnel under force health protection programs of the Department of Defense?
 - (b) Is the activity an authorized health and medical activity as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment?
 - (c) Is the activity performed for the sole purpose of medical quality assurance?
 - (d) Is the activity performed solely for an operation test & evaluation (OT&E) project where the activities and project meet the definition of OT&E?
 - (e) Is the activity performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units, including such activities as occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information?
 - (f) Is the activity, including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of government officials responsible for the operation or oversight of the program being evaluated and are not intended for generalized use beyond such program?
 - (g) Are the survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by DoD Directive 5240.01?
- (4) Does the activity involve Human Research as defined in FDA regulations? **ANY of these activities are research involving human subjects:**
- (a) The activity is conducted in the United States and will involve the use of a test article [21CFR 56.102(l)] in one or more persons that is **NOT** the use of an approved drug in the course of medical practice. [21 CFR 50.3(c)]
 - (b) Data regarding subjects or control subjects will be submitted to or held for inspection by FDA as part of an application for a research or marketing permit. [21 CFR 56.102(c)]
 - (c) Data regarding the use of a device on human specimens (living or dead) will be submitted to or held for inspection by FDA as part of an application for a research or marketing permit. [21 CFR 56.102(c)]

4.2 IRB initial review of research. All human subjects research must be reviewed at a convened IRB meeting unless determined either to meet criteria for exemption or qualify for expedited review [32 CFR 219.101(b) and 32 CFR 219.108(b)].

4.2.1 Convened IRB. The IRB conducts initial review for non-exempt human subjects research at convened meetings unless the IRB Chair or Vice Chair determines the research may be eligible for expedited initial review.

4.2.2 Expedited review. The IRB may use an expedited review process to review studies that meet the categories adopted by the Department of Defense (DoD) and DON and that involve no greater than “minimal risk” categories described in Federal Register: November 9, 1998 (Volume 63, Number 216) pages 60364-60367.]

4.2.2.1 IRB Chair and Vice Chair review and authority. In accordance with SECNAVINST 3900.39D, paragraph 8f, IRB Chairs and Vice Chairs, if delegated authority from the research approval authority, may review and make recommendations for research that meets criteria for expedited review procedures. The IRB Chair/Vice Chair exercises the full range of authority of the IRB except disapproval of research; only the convened IRB may disapprove research. The IRB Chair/Vice Chair ensures that the informed consent process and documentation of informed consent are carried out unless the IRB waives or alters the requirements per federal regulations. All expedited reviews must be reported to the IRB for research approved under this procedure [32 CFR 219.110(2)(c)]. The IRB Chair/Vice Chair must not conduct the review of research when doing so creates a conflict of interest [32 CFR 219.107(e)].

4.2.3 Approval criteria. Per 32 CFR 219.111, to recommend approval of research the IRB must determine that:

- a. Risks to subjects are minimized:
 - (i) By using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
 - (ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within its authority.
- c. Selection of subjects is equitable. In making this assessment the IRB should

take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly aware of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

d. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 32 CFR 219.116.

e. Informed consent will be appropriately documented, per, and to the extent required by 32 CFR 219.117.

f. When appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.

g. When appropriate, there are adequate safeguards for the privacy of subjects and to maintain the confidentiality of data.

h. When some or all of the subjects are likely to be vulnerable to coercion or undue influence (children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), additional protections for the rights and welfare of these subjects have been included in the study. (See paragraph 4.6 for additional requirements for DoD personnel as subjects.)

4.2.4 Determining the frequency of continuing review. As specified in 32 CFR 219.109, the IRB shall conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The approval period should be documented clearly in the IRB meeting minutes or IRB records. DON IRBs should consider the following when determining an appropriate interval for continuing review:

- a. Nature of any risks posed by the research;
- b. Uncertainty regarding risk;
- c. Vulnerability of the subject population;
- d. Experience of the investigators in conducting research; the IRB's previous experience with the investigators (e.g., compliance history, problems obtaining informed consent, or complaints from subjects);
- e. Projected rate of enrollment; and
- f. Whether the research involves novel interventions.

4.2.5 Effective date of approval. The date the institutional official (IO) approves a

project may differ from the date the IRB recommends approval. The effective date of approval is the date the IO approves the research. If the IRB determines that annual continuing review is appropriate relative to the degree of risk, the continuing review date, also referred to as the expiration date, is based on the date the IRB recommends approval or modifications to secure approval, not the date the IO approves the research. For example, the IRB recommends approval on 15 March 2011 and determines that annual review should be conducted on 14 March 2012; the IO approves the research on 15 April 2011. The effective dates of approval are 15 April 2011 through 14 March 2012. Command approval of the research expires at 2400 on 14 March 2012.

4.2.6 Review of collaborative or cooperative research. DON commands may collaborate with each other, other DoD agencies, non-DoD federal agencies, and non-federal institutions. Each command engaged (DoD Instruction 3216.02, Glossary Part II) in the collaborative or cooperative research effort is responsible for safeguarding the rights and welfare of human subjects and for complying with the requirements of 32 CFR 219.

4.2.6.1 Duplication of reviews. Each DON command participating in a collaborative project may conduct an independent IRB review of the research. However, DoD Instruction 3216.02, enclosure 3, section 1, subparagraph 1c(4), requires that duplication of review be justified in any collaboration with other DoD components.

4.2.7 Communicating the IRB's initial review determination to the command and investigators.

4.2.7.1 IO notification. IRB recommendations are communicated to the IO of the command holding the DON assurance for IO approval.

4.2.7.2 PI notification. Following IO approval, the PI must be notified of the initial review determinations. If the determination is to approve the research, the communication should indicate the date of approval, the expiration date or date of next review, and the level of review (e.g., expedited or convened board). If the determination is to disapprove, the communication must indicate the reason(s) for disapproval. The investigator shall be given an opportunity to respond in writing or in person [32 CFR 219.109(d)].

4.2.7.3 Policies and procedures. Commands should follow a written procedure for communicating IRB findings and recommendations to the IO, documenting IO action, and communicating results to the PI.

4.2.8 PI responsibilities. SECNAVINST 3900.39D, paragraph 8g, stipulates that the PI is responsible for:

- a. Obtaining IRB review and command approval prior to conducting research;
- b. Following policies and procedures for initial IRB review and command approval of research;

- c. Submitting information and materials required by the IRB;
- d. Complying with effective dates of institutional approval including the expiration date.

4.3 Scientific review. Research involving human subjects must conform to generally accepted scientific principles [32 CFR 219.111(a)(1)(i)] and should be based on a thorough knowledge of the scientific literature and other relevant sources of information.

4.3.1 Regulatory requirements. DoD Instruction 3216.02 and SECNAVINST 3900.39D require scientific or scholarly review before the IRB can recommend approval of research involving human subjects.

4.3.1.1 DoD Instruction 3216.02, enclosure 3, section 3, subparagraph 3a(2) requires DoD institutions to establish policies and procedures to require scientific review of non-exempt research involving human subjects and to ensure this review is considered during the IRB review process. It is recommended that scientific review be conducted for research involving human subjects determined to be exempt.

4.3.1.2 SECNAVINST 3900.39D, paragraph 8c(6) requires that commanders, commanding officers, and officers in charge ensure an independent review of research for scientific merit or scholarship prior to IRB review.

4.3.2 Policies and procedures. DON commands should have policies and procedures that describe the command's process for evaluation of the proposed research for scientific or scholarly merit. Policies and procedures should:

- a. Indicate who is responsible for scientific review, how the review is documented and communicated.
- b. Indicate that individuals are prohibited from conducting scientific reviews of research in which they have a conflict of interest.
- c. Determine whether amendments to previously approved research, which could affect the scholarly or scientific merit of a protocol, should undergo scientific review prior to IRB review.

4.3.3 Scientific review process. Personnel conducting scientific reviews should consider the following:

- a. Is the objective/hypothesis of the research stated clearly?
- b. Does the data collection plan adequately address the objective/hypothesis?
- c. Are sufficient subjects available to support the research?

- d. Does the study address an important problem?
- e. How will scientific knowledge be advanced if the study goals are achieved?
- f. What impact will the study have on the concepts and methods already in use in the field?
- g. Are the conceptual framework, design, methods, and analytical approach adequate to the aims of the research?
- h. Does the investigator recognize and acknowledge potential problem areas and consider alternatives?
- i. Is the study design scientifically sound?
- j. Is the work proposed appropriate to the experience and training of the PI and any associate investigators (AIs) or other researchers engaged in the study?

4.3.4 Consistent with SECNAVINST 3900.39D, paragraph 8c(17), documentation of completion of scholarly or scientific reviews are submitted to DON HRPP for headquarters-level review as part of submission of research protocol and supporting documentation.

4.4 Research monitor. A research monitor is an individual with expertise consonant with the nature of risks associated with a research protocol, and they shall be independent of the research team conducting the research involving human subjects. Their primary role is to protect the safety and well-being of human subjects [DoD Instruction 3216.02, enclosure 3, section 8a(4)].

4.4.1 Regulatory requirements. DoD and FDA regulations require the following:

4.4.1.1 In order to approve research, the IRB shall determine whether the research plan, when appropriate, makes adequate provision for monitoring the data collected to ensure the safety of subjects [32 CFR 219.111(a)(6); 21 CFR 56.111(a)(6)].

4.4.1.2 For DoD-conducted research involving human subjects determined by the IRB to involve more than minimal risk to human subjects, the IRB shall approve an independent research monitor by name (DoD Instruction 3216.02, enclosure 3, section 8a). Additionally, the research monitor may be identified by an investigator or appointed by an IRB or IO for research involving human subjects determined to involve minimal risk. (DoD Instruction 3216.02, enclosure 3, section 8).

4.4.2 Policies and procedures. Policies and procedures (sample included in Table II):

TABLE II. SAMPLE COMMAND POLICY FOR RESEARCH MONITOR

1. For research involving human subjects determined by the IRB to involve more than minimal risk to human subjects, the IRB shall approve an independent research monitor by name.
2. The research monitor may be identified by an investigator or appointed by the IRB or IO for research involving human subjects determined to involve minimal risk.
3. The duties of the research monitor shall be determined on the basis of specific risks or concerns about the research.
4. 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 UPIRTSO reports; and oversee data matching, data collection, and analysis) and report his/her observations and findings to the [Insert either - IRB or a designated official].
5. Research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol.
6. Research monitors shall be independent of the team conducting the research involving human subjects.
7. There may be more than one research monitor (e.g., if different skills and/or range and type of experience are necessary).
8. The monitor may be an ombudsman or a member of the Data Safety Monitoring Board.
9. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others not involved in the study about the research.
10. Research monitors shall have the responsibility to report their observations and findings promptly to the [State either - IRB or other designated official]. They shall have the authority to:
 - a. Stop a research study in progress;
 - b. Remove individual subjects from a study;
 - c. Take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the research monitor's report.
11. The IRB must approve a written summary of the monitor's authority, duties, and responsibilities and cite them in IRB minutes or records.

**TABLE II. SAMPLE COMMAND POLICY FOR RESEARCH MONITOR
(Continued)**

12. The [Insert either - IRB or HRPP official] shall communicate with research monitors via [email, letter] to confirm their authority, duties, and responsibilities.

13. The [Insert person/role] shall include the communication of research monitor duties in the IRB records.

14. The Heads of the OSD and DoD Components may waive the requirement to have a research monitor on a case-by-case basis when the inclusion of a research monitor is not necessary to provide additional protections for human subjects. Waivers must be coordinated with the DON HRPP.

4.5 Data safety monitoring plan (DSMP). The safety of the study participants and the risks versus benefits should be monitored throughout the study period. Monitoring may be conducted in various ways or by various individuals or groups, depending on the risks of the research.

4.5.1 Regulatory requirements and guidance. Federal regulations and guidance require that research include adequate plans for monitoring. Applicable regulations and guidance include:

4.5.1.1 32 CFR 219.111 (a)(6) and 21 CFR 56.111(a)(6) require that, when appropriate, research plans make adequate provisions for monitoring the data collected to ensure the safety of subjects.

4.5.1.2 21 CFR 50.24(a)(7)(iv) requires additional protections for FDA-regulated emergency research, including the establishment of an independent data monitoring committee to exercise oversight of the clinical investigation.

4.5.2 Investigator/key personnel responsibilities. For studies involving greater than minimal risk, investigators should develop a DSMP that adequately provides for monitoring the data collected to ensure the safety of subjects. DoD Instruction 3216.02, enclosure 3, section 8 requires the appointment, by name, of an independent research monitor who has expertise consonant with the nature of the risks of the research, and the specific duties that the research monitor will perform. If the research is a clinical trial that is greater than minimal risk, the DSMP also may include the appointment of a Data Safety Monitoring Board (DSMB).

4.5.3 When a data safety monitoring plan should be used. 32 CFR 219.111 (a)(6) requires the IRB to determine that research plans, when appropriate, make adequate provisions for monitoring collected data to ensure the safety of subjects.

4.5.3.1 Minimal Risk. The regulations require adequate provisions for monitoring collected data to ensure the safety of subjects when appropriate. An IRB may determine that minimal risk research does require a DSMP. The IRB may determine that a

DSMP is necessary when research involves obtaining sensitive information.

4.5.3.2 Clinical Investigations Involving Greater than Minimal Risk. A DSMB (in addition to a research monitor) may be required for research involving greater than minimal risk. A DSMB should be used for “clinical investigations,” as defined in DoD Instruction 3216.02, Glossary Part II., involving high-risk interventions, vulnerable populations, or blinded or multi-center study designs. Emergency research that is regulated by the FDA requires additional protections, including establishment of an independent data monitoring committee for oversight of the clinical investigation [21 CFR 50.24(a)(7)(iv)]. The research monitor may be a member of the DSMB (DoD Instruction 3216.02, enclosure 3, section 8a).

4.5.4 Elements of a Data Safety Monitoring Plan. The elements of a DSMP will vary based on the risks, complexity, and design of the research. An IRB may require the following elements, depending on the research:

- a. The type of information to be collected for data monitoring purposes;
- b. Persons or parties responsible for monitoring data;
- c. The frequency of collecting and assessing data for monitoring purposes;
- d. An explanation of rules that will determine when specific actions will be required, such as stopping the research; and
- e. Procedures for reporting results of the data monitoring to the IRB, investigators, command officials, or others;

4.5.5 Policies and Procedures. Each command should include instructions for reviewing the DSMP in their policies and procedures. These instructions should describe:

- a. When the IRB should consider implementing provisions for monitoring data to ensure the safety of subjects;
- b. Procedures for having DSMP materials reviewed by the IRB, including any documents that describe such provisions; and
- c. Procedures for the IRB determining that the DSMP is adequate.

4.5.6 IRB Responsibilities. Per 32 CFR 219.111, the IRB shall determine whether the research plans adequately address the monitoring of data collected to ensure the safety of subjects. To do so, the IRB should consider carefully:

- a. The potential risks involved in the research;
- b. The subject population;

- c. The nature and complexity of the research;
- d. The research design; and
- e. Effective approaches to monitoring subject safety.

If the IRB determines that the provisions to monitor the safety of subjects are inadequate, it should request that specific elements be added to the DSMP. The IRB determination of whether the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects, and any additional provisions that the IRB requires, should be documented in the IRB meeting minutes.

4.6 DoD personnel (DoD civilian employees and members of the military Services) as subjects. The perception of undue influence or coercion to participate in research involving human subjects must be avoided. Special consideration must be given to the recruitment process for Service members and DoD civilian employees [DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7(e) and SECNAVINST 3900.39D, paragraph 6a(6)].

4.6.1 Military Personnel as Subjects.

4.6.1.1 The IRB may require that PIs obtain confirmation that the Service member's command supports the member's participation in DoD-supported research involving human subjects while on-duty. This may be satisfied by obtaining a letter of support from the cognizant commander. Additionally a Service member's ability to perform his or her military duties may be affected by participating during off-duty time (i.e., on leave or during non-duty hours). Per DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7e(1)(a), Service members shall follow their component and command's policies for approving off-duty employment or activities.

4.6.1.2 Regardless of the risk level of the research, superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel, and equivalent civilians) regarding participation as subjects in research involving human subjects. Peer pressure should also be considered and minimized (SECNAVINST 3900.39D, paragraph 6).

4.6.1.3 Superiors (unit officers, senior NCOs, and equivalent civilians) in the chain of command shall 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, supervisors so excluded shall be afforded the opportunity to participate as human subjects in separate recruitment sessions [DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7e(1)(c)].

4.6.1.4 For research involving Service members as human subjects that has been determined to be greater than minimal risk and when recruitment occurs in a group setting,

the IRB shall appoint an ombudsman [DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7e(1)(d)]. The ombudsman shall not be associated in any way with the research and shall be present during the recruitment in order to ensure that the voluntary involvement or recruitment of the Service members is adequately stressed and that the information provided about the research is clear, adequate, and accurate. The IRB shall determine whether it is appropriate to appoint an ombudsman to ensure voluntary recruitment, when it occurs in a group setting, for research involving Service members as human subjects that is found to be not greater than minimal risk. The decision to appoint an ombudsman should be based in part on the human subject population, the consent process, and the recruitment process.

4.6.2 DoD Civilians as Subjects.

4.6.2.1 The IRB may require that PIs obtain confirmation in writing that the DoD civilian's command supports member's participation in DoD-supported research involving human subjects while on duty. This may be satisfied by obtaining a letter of support from the cognizant commander. Per DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7e(2)(a), DoD civilians should follow their component and command's policies for participation in research involving human subjects.

4.6.2.2 Per SECNAVINST 3900.39D, paragraph 6a(6), supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research involving human subjects.

4.6.2.3 Per DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7e(2)(c), supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) shall not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in separate recruitment sessions.

4.6.2.4 Per DoD Instruction 3216.02, enclosure 3, section 7, subparagraph 7e(2)(d), research involving civilians as human subjects and when recruitment occurs in a group setting, the IRB shall discuss appointing an ombudsman. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

4.6.3 Investigator Responsibilities. The protocol submitted to the IRB should provide sufficient information about the recruitment and consent processes for the IRB to be able to make a determination that the requirements for including DoD personnel in research have been met.

4.6.4 IRB Responsibilities. The IRB's determination of whether these requirements have been met should be included in the minutes or expedited IRB review documents for research involving DoD personnel as human subjects.

4.7 The Use of Humans as Experimental Subjects. The DoD Instruction 3216.02 defines research involving a human being as an experimental subject as an activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. Research involving a human being as an experimental subject and utilizing DoD appropriated funds must comply with 10 USC Section 980.

4.7.1 Informed Consent with Experimental Subjects. 32 CFR 219.116 identifies the conditions under which the IRB may waive informed consent. However, 10 USC Section 980 imposes limitations on waiving informed consent when using DoD appropriated funds. When using DoD appropriated funds in research involving experimental subjects, consent must be obtained in advance from the experimental subject. If the subject cannot consent, consent may be obtained in advance from the subject's legally authorized representative if the research is intended to benefit the subject. If there is no direct benefit intended for the experimental subject, consent can only be obtained from the subject. ASD(R&E) may waive the requirement for prospective consent if the following conditions are met:

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

4.7.2 Exempt Research. The DoD definition (DoD Instruction 3216.02, Glossary Part II) of experimental subject does not apply to research activities that meet the exemption criteria at 32 CFR 219.101(b).

4.7.3 Level of Risk. As specified in DoD Instruction 3216.02, Glossary, Part II., 10 USC Section 980 must be considered for all non-exempt research (both minimal risk and greater than minimal risk).

4.7.4 Minors as Experimental Subjects. 10 USC Section 980 applies to children as well as adults. As such, the intent of the research must be to benefit directly the individual child and prospective consent must be obtained from the parent or legally authorized representative.

4.7.5 Retrospective Research. As specified in DoD Instruction 3216.02, Glossary, Part II., experimental subject does not apply to research involving the collection or study of existing data, documents, records, or specimens from living individuals.

4.8 The informed consent process. Voluntary informed consent is fundamental to ethical research with humans. Unless a waiver of consent is granted by the IRB per 32 CFR 219.116, or

per 10 USC Section 980 for research involving a human being as an experimental subject, no investigator may involve a human subject in research unless the subject is a volunteer and the investigator has obtained informed consent from the subject or the subject's legally authorized representative.

4.8.1 Investigator description of the consent process. Applications or other materials submitted to the IRB should have sufficient information regarding the consent process, including:

- a. The person who will obtain informed consent;
- b. The person who will provide consent or permission;
- c. Any waiting period between informing the prospective subject and obtaining consent;
- d. Steps taken to minimize the possibility of coercion or undue influence;
- e. The language used by those obtaining consent;
- f. The language understood by the prospective subject or the legally authorized representative; and
- g. The information to be communicated to the prospective subject or the legally authorized representative.

4.8.2 IRB review of consent process. The IRB determines that the regulatory criteria for the consent process are met. These include the following:

- a. The investigator will obtain the legally effective consent of the subject or the subject's legally authorized representative;
- b. The circumstances of the consent process provide the prospective subject or the legally authorized representative sufficient opportunity to consider whether to participate;
- c. The circumstances of the consent process minimize the possibility of coercion or undue influence;
- d. Information provided to the subject or the legally authorized representative during the consent process will be in language understandable to the subject or the representative;
- e. The information being communicated to the subject or the representative during the consent process will not include exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's

legal rights; releases or appears to release the investigator, the sponsor, the command, or its agents from liability for negligence.

4.9 Consent Readability. 32 CFR 219 requires that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The information that is given to the subject or the representative is to be in language understandable to the subject or the representative. The readability of the consent document can be increased by avoiding the following: technical language, "legalese," medical jargon, long and complex sentences, words greater than two syllables, the use of upper case, and contractions. More information is available at: www.med.navy.mil

4.10 Waiver or alteration of informed consent and waiver of informed consent documentation. Under certain circumstances, an investigator is permitted to request a waiver of informed consent, alteration of specific elements of consent, or waiver of documentation of consent. In each instance, a rationale should be provided to the IRB for requesting the waiver or alteration. Research involving a human being as an experimental subject and utilizing DoD appropriated funds must comply with 10 USC Section 980.

4.10.1 Criteria for waiver or alterations. Two sets of independent criteria are available for waiving or altering consent. Each set is independent. Criteria at 32 CFR 219.116(d) are more commonly used.

4.10.1.1 32 CFR 219.116(d). An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

- a. The research involves no more than minimal risk to the subjects (see the regulatory definition of "minimal risk.");
- b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- c. The research could not practicably be carried out without the waiver or alteration; and
- d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation (for example, debriefing at the conclusion of a study involving deception).

4.10.1.2 32 CFR 219.116(c). An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that the research is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

- a. Public benefit of service programs;
- b. Procedures for obtaining benefits or services under those programs;
- c. Possible changes in or alternatives to those programs or procedures; or
- d. Possible changes in methods or levels of payment for benefits or services under those programs; and
- e. The research could not practicably be carried out without the waiver or alteration.

4.10.2 Criteria for waiver of documentation of consent. The criteria for waiving consent documentation are at 32 CFR 219.117(c), and for FDA regulated research, at 21 CFR 56.109(c)(1). In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

4.10.2.1 32 CFR 219.117(c). An IRB may waive the requirement for the investigator to obtain a signed informed consent document for some or all subjects provided that:

- a. The only record linking the subject and the research would be the consent document. The principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether he or she wants documentation linking the subject with the research, and the subject's wishes will govern; or
- b. The research presents no more than minimal risk of harm to subjects (see the regulatory definition of "minimal risk.") and involves no procedures for which written consent is normally required outside of the research context.

4.10.2.2 21 CFR 56.109(c)(1). An IRB shall require documentation of informed consent per 21 CFR 50.27, except as follows: The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that:

- a. The research presents no more than minimal risk of harm to subjects; and
- b. Involves no procedures for which written consent is normally required outside the research context.

4.10.3 IRB Responsibilities. The determination to waive or alter informed consent or waive the requirement for the investigator to obtain a signed consent form may be made by the

convened IRB or by the IRB Chair/Vice Chair using expedited procedures, if eligible.

4.10.3.1 In accordance with 32 CFR 219.116(d), the convened IRB or the expedited reviewer must document that a waiver/alteration is being applied.

4.10.3.2 Determinations should be documented in the IRB minutes or using forms or checklists that become part of the IRB records. (Contact DON HRPP for an example of a checklist.)

4.10.3.3 Documentation should include a statement that the requirements for the waiver/alteration were met.

4.10.4 10 USC Section 980. As specified at 10 USC Section 980, there are limitations for waiver of informed consent for research involving a human being as an experimental subject. (See section 4.7 and 4.8).

4.10.5 Planned emergency research. As specified at 21 CFR 50.20, no investigator may involve a subject in FDA-regulated research involving the use of a drug, device, or biologic unless the investigator has obtained legally effective informed consent except for the emergency use of a test article or planned emergency research. Refer to 21 CFR 50.23 and 50.24 for requirements. Note that 10 USC Section 980 requirements may also apply in planned emergency research.

4.11 IRB required modifications to secure approval. An IRB must review proposed research, including proposed changes to previously approved research, at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except when expedited review is authorized. For research to be recommended for approval, it must receive the approval of a majority of those members present at the meeting [32 CFR 219.108(b)]. An IRB shall review and have authority to recommend approval, require modifications in (to secure approval), or disapprove all research activities covered by 32 CFR 219 and 21 CFR 50 [32 CFR 219.109 and SECNAVINST 3900.39D, paragraph 8e].

4.11.1 IRB Actions. Given the authorities that IRBs have under 32 CFR 219.109(a), when conducting an initial or continuing review of a research study, or a review of proposed changes to a previously approved research study, an IRB can take any of the following actions:

- a. Recommend approval of the research study or proposed changes;
- b. Require modifications to secure approval; or
- c. Disapprove the research study or proposed changes.

4.11.2 Modifications to Secure Approval: “Approval with Conditions” vs. “Deferral.” An IRB may recommend approval of research “with conditions” if, given the conditions, the IRB

is able, if the conditions are satisfied, to make all of the determinations required for approval under 32 CFR 219.111 and, if applicable, subparts B, C, or D of 45 CFR 46 as amended by the DoD Instruction 3216.02. This applies to the IRB's initial and continuing review of research, and review of changes proposed to previously approved research. The final determination of whether conditions have been met may be made by the IRB Chair or Vice Chair. If the IRB is unable to make all the determinations required for approval under 32 CFR 219.111 and needs further information, the protocol must be deferred for convened board review.

4.11.3 Examples of approval with conditions. The IRB may require the following as conditions of approval of research:

- a. Confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (confirmation that the research excludes children);
- b. Submission of additional documentation (certificate of HSR training);
- c. Precise language changes to protocol or informed consent documents; and
- d. Substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

4.11.4 Examples of requirements for modification that should be returned to the convened board for review. The following are examples of concerns the IRB may convey to the investigators when the IRB has been unable to determine that the criteria for approval at 32 CFR 219.111 have been met:

- a. Clarification of stopping criteria;
- b. Questions about how referrals will be obtained; how subjects will be identified; measures to ensure subject privacy; and the plan for research related injuries;
- c. Name and/or qualifications of the research monitor; and
- d. Requests for justification of the number of subjects.

Note: Any request that begins with "clarify," "describe," "explain," "how," or "provide more information" typically are not eligible for approval with conditions.

4.12 Unanticipated problems involving risks to subjects or others (UPIRTSO). This guidance is intended to assist DON Investigators, IRBs, and commands in understanding their responsibilities associated with the reporting of unanticipated problems involving risk to subjects or others (UPIRTSOs) that occur in research conducted or supported by the DON.

4.12.1 Regulatory requirements. Federal regulations [32 CFR 219.103(b)(5) and 21

CFR 56.108(b)(1)] require institutions supporting and conducting research to ensure that investigators promptly report “any unanticipated problems involving risk to subjects or others (UPIRTSO).” As defined in DoD Instruction 3216.02, Glossary Part II., a UPIRTSO is any incident, experience, or outcome that meets all three of the following conditions:

- a. Is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied.
- b. Is related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- c. Suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

4.12.2 Policies and procedures. DON IRBs must have written procedures for ensuring that Investigators, IRBs, and IOs fulfill their regulatory responsibilities in promptly reporting and handling internal and external UPIRTSOs [32 CFR 219.103(5)].

4.12.2.1 Reporting requirements for internal UPIRTSOs. An internal UPIRTSO is any problem/event involving research subject(s) at a command for which the DON IRB serves as the IRB of record.

a. Investigator. The investigator must notify the IRB in writing of UPIRTSOs [SECNAVINST 3900.39D paragraph 8g(6)]. A UPIRTSO should be reported to the IRB as soon as the investigator becomes aware of it.

b. IRB. The IRB must report any UPIRTSO to the commander, commanding officer, or officer in charge in his role as the IO [SECNAVINST 3900.39D paragraph 8e(6)]. A UPIRTSO should be reported to the IO within 24 hours of receipt of the investigator report and provide updates until resolved.

c. IO. The IO must report UPIRTSOs to the Director, DON HRPP [SECNAVINST 3900.39D paragraph 8c(23)(a)]. A UPIRTSO should be reported to the Director, DON HRPP within 72 hours of receipt of the IRB/investigator report and should provide updates until resolved.

4.12.2.2 Reporting requirements for external UPIRTSOs. An external UPIRTSO is any problem/event involving research subjects enrolled by other institutions in multicenter research projects that fall under the purview of an external IRB. Investigators, IRBs, and IOs are required to report external UPIRTSOs.

- a. Command. The command should establish a policy for reporting external UPIRTSOs. Command policy should require external UPIRTSOs be reported at minimum at the time of the next continuing review for the study.
- b. Investigator. The investigator should report external UPIRTSOs to the IRB per command policy.
- c. IRB. The DON IRB should acknowledge receipt of the investigator's report, and review it to determine if further action is necessary.

4.12.3 IRB responsibilities. DON IRBs should review the investigator's report of the event submission to determine if the problem or event meets the criteria to be considered a UPIRTSO. The IRB should determine if the corrective actions taken by the investigator are adequate and appropriate. When reviewing a report of a UPIRTSO, the IRB should consider whether the affected research protocol still satisfies the requirements for approval under 32 CFR 219.111.

4.12.4 IRB corrective actions. IRBs may require additional corrective action or changes to research in the event of an UPIRTSO. Examples of corrective actions or substantive changes that might need to be considered in response to an UPIRTSO include:

- a. Changes in informed consent documents;
- b. Changes in the protocol or other study documents;
- c. Modification of the inclusion or exclusion criteria;
- d. Re-consenting or informing current or previously enrolled research subjects (to occur whenever the information may relate to subjects willingness to continue participation in the research);
- e. Steps to reduce any immediate risks to subjects or others;
- f. Modifying the continuing review schedule;
- g. Suspending or terminating the research study;
- h. Requesting more information pending a final decision;
- i. Referring to other organizational entities (e.g., legal counsel, risk management); and
- j. Taking other actions appropriate for the local context.

4.12.5 IO. The IO must assure the reporting of UPIRTSOs to the Director, DON HRPP, and appropriate sponsors and/or agencies [SECNAVINST 3900.39D paragraph

8c(23)(a)]. Supporting documentation of the assessment, outcome, and any subsequent actions should be provided. Any human subject research subject to FDA regulations must adhere to reporting requirements of 21 CFR 56.

4.12.6 Investigator responsibilities. It is the responsibility of the investigator to:

- a. Determine if a given problem/event may be an UPIRTSO;
- b. Consult with the IRB on issues relating to the UPIRTSO determination as necessary; and
- c. Report external UPIRTSOs per command IRB policy.

4.12.7 Investigator reports. Investigator reports to the IRB should include:

- a. A detailed description of the problem or event;
- b. A detailed description of outcome of the event/problem for the subject, treatment provided to subject, the subject's recovery, and planned follow-up on subject's conditions related to the event/problem;
- c. A corrective action plan or justification for why a plan is not needed;
- d. Any relevant documents or reports with the subject's identifying information removed; and
- e. A modification request to the IRB if the protocol or consent document requires revisions.

4.13 Policies and procedures for review of changes to previously approved greater than minimal risk research. DoD and FDA regulations require that:

a. IRBs establish written procedures in order to ensure prompt reporting to the IRB of any changes in a research activity previously approved. Such changes require IRB review and command approval prior to implementation, except when necessary to eliminate immediate hazards to the subject.

b. 32 CFR 219.110 states that an IRB may use the expedited review procedure to review:

(1) Some or all of the research appearing on the list at Title 63, Federal Register 60364–60367 of 9 Nov 98 and found to involve no more than minimal risk; and/or

(2) Minor changes in previously approved research during the period for which approval is authorized (1 year or less).

4.13.1 HRPP policies. HRPP policies and procedures should:

a. Define substantive changes that require review and approval by the convened IRB.

b. Define “minor” changes that may be reviewed by expedited procedures. “Minor” changes do not include procedures that are more than minimal risk or do not fall into the categories (1) through (7) at Title 63, Federal Register 60364–60367 of 9 Nov 98 that can be reviewed by the expedited procedure. In addition, minor changes do not involve any significant change in:

- (1) Risk to participants;
- (2) Methods, aims or procedures;
- (3) The risk/benefit ratio; or
- (4) To the study population size or composition.

4.13.2 Examples of minor changes. Examples of changes that may be considered “minor” include, but are not limited to:

a. Decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations;

b. A decrease in the duration or number of study visits, provided that such a decrease does not affect the collection of information related to safety evaluations;

c. Addition of translations of previously approved materials (e.g., informed consent document, recruitment materials, etc.).

4.13.3 Examples of changes that are not considered minor changes. Examples of changes not considered eligible for review using the expedited procedure may include, but are not limited to:

a. The addition to the informed consent document of a description of serious unexpected adverse events or other risks;

b. Changing the inclusion criteria;

c. Narrowing the range of exclusion criteria;

d. The deletion of laboratory tests, monitoring procedures, or study visits directed at the collection of information for safety evaluations;

e. Changes, which, in the opinion of the IRB Chair/designee, do not meet the criteria or intent of a minor modification; and

f. The addition or removal of a principal investigator or research monitor.

4.14 Continuing review procedures. Continuing review of research is an essential requirement for the protection of human subjects. DON IRBs must conduct continuing review of research covered by 32 CFR 219.

4.14.1 Continuing review intervals. Continuing review of human subject research must be conducted at intervals appropriate to the degree of risk, but at least annually, as long as the project continues to involve human subjects [32 CFR 219.109(e)]. DON HRPP considers a research project to involve human subjects as long as the investigators continue to:

a. Obtain data about the subjects through intervention or interaction; or

b. Obtain, use, study, or analyze identifiable private information about the subjects. Once all such activities described in the approved protocol are completed, continuing review no longer is required.

4.14.2 Expedited continuing review. An IRB may use an expedited review procedure to conduct continuing review of research for some or all of the research appearing on the list of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk. Under an expedited review procedure, the review may be carried out by the IRB Chair or Vice Chair if given that authority by the IO. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not recommend disapproval of the research. For any research approved under an expedited review procedure at the time of continuing review, all IRB members must be advised of such approvals (32 CFR 219.110 and SECNAVINST 3900.39D, paragraph 8f).

4.14.3 Continuing review criteria. The criteria for recommending approval of research under 32 CFR 219.111 applies to both initial and continuing review. When conducting continuing review, the IRB also should consider any new information (from the investigator or other sources) that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. (See Table III for policies and procedure content.)

4.14.3.1 Risks to subjects. When assessing risk at continuing review, the IRB should start with the presumption that the research, as previously approved, satisfies all of the criteria at 32 CFR 219.111. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document. When conducting continuing review and evaluating whether research continues to satisfy the criteria for IRB approval of research, IRBs should pay particular attention to the following four aspects of the research:

- a. Risk assessment and monitoring;
- b. Adequacy of the process for obtaining informed consent;
- c. Investigator and institutional issues; and
- d. Research progress.

4.14.3.2 Subject selection. When assessing subject selection and recruitment, an IRB should consider:

- a. Selection of subjects continues to be equitable;
- b. All current recruitment methods have been approved by the IRB and remain adequate;
- c. No superiors, military or civilian, shall not have influenced a subordinate's decision to participate or continue participation (SECNAVINST 3900.39D, paragraph 6); and
- d. Safeguards for other subjects likely to be vulnerable to coercion or undue influence are in place and remain adequate.

4.14.3.3 Consent. An IRB should confirm the process for obtaining informed consent remains voluntary, non-coercive, informative, and equitable. When reviewing informed consent documents, the IRB determines, as appropriate:

- a. The Informed Consent Document (ICD) is the most recently approved version. If modifications are submitted, the ICD must include all the general requirements of informed consent in accordance with the 32 CFR 219.116;
- b. Informed consent has been obtained from each subject or the subject's legally authorized representative and properly documented;
- c. New information available about the research that could affect a potential subject's decision to participate or continue participation has been included in the consent;
- d. No new information is available that requires modification to the informed consent process; and
- e. If the IRB has approved an alteration of, or waived the requirement for informed consent and/or documentation of informed consent, the IRB verifies that the provisions for granting the waiver remain in place.

4.14.3.4 Investigator status. An IRB should have current information regarding the status of the PI, the research location, and the research staff to ensure that there has been no changes that may affect the subjects' safety, privacy, or confidentiality. An IRB should consider, as appropriate:

- a. Any modifications to the approved research protocol that may affect subject safety or information available to the subject;
 - b. The PI's standing regarding duty station, employer, certifications, research compliance, and legal issues;
 - c. The PI's ability to devote time to continue the research;
 - d. The status and merit of any complaints, investigations, or correspondence about research conduct related to the PI or research location;
 - e. The merit of correspondence concerning subject safety or risks related to the PI or research location;
 - f. Any reports or evidence of deviations from the approved protocol;
- and
- g. Any reports or evidence of non-compliance with applicable federal regulations.

4.14.3.5 Study status. An IRB should evaluate the research progress and confirm that the information submitted remains consistent with the approved protocol and does not require either modification to the consent process or that additional information be provided to the subject. The research progress also should reflect the status of all enrolled subjects and the circumstances regarding all subject withdrawals. The IRB should consider:

- a. Whether the information submitted by the PI is consistent with the protocol;
- b. The number of UPIRTSOs as defined in the DoD Instruction 3216.02, part II Definitions, adverse events [SECNAVINST 3900.39D enclosure (1)] and serious adverse events [21 CFR 312.32(a)] reported;
- c. Whether the number of enrolled subjects corresponds to the projected number of enrolled subjects, and if enrollment is consistent with the planned number of subjects described in the approved protocol;
- d. The diversity of enrolled subjects based on gender, ethnicity, economic status, or other factors; and

e. The number of subjects who withdrew from the study and reasons for withdrawal.

4.14.4 IO responsibility. The IO is responsible for reviewing recommendations of the IRB and for approving continuation of research. Following IRB review and recommendations for approval, the IO may approve, require modifications to gain approval, or disapprove continuation of current research protocols; require additional safeguards, suspend or terminate the research based on specific criteria and the IRB's continuing review findings or the IRB Chair's written recommendations for research eligible for expedited review. The IO may not approve the continuation of research if the IRB recommends disapproval [SECNAVINST 3900.39D, paragraph 8.c.(15)].

4.14.5 Determining the Frequency of Continuing Review. At the time of initial approval and continuing review, the IRB should specify duration of the approval period, which can be a time interval or other threshold such as number of subjects. At continuing review, IRBs should consider whether the frequency for continuing review is adequate or should be adjusted.

4.14.6 Effective date of approval. (See 4.2.5.)

Note: DON HRPP recognizes the logistical advantages of keeping the expiration date of the approval period constant from year to year throughout the life of a research project. Therefore, when (a) the IRB recommends approval for one year at the time of each continuing review, and (b) the IRB performs continuing review and recommends re-approval of the research within 30 days before the approval period expires, the IRB may retain the anniversary of the expiration date of the initial approval as the expiration date of each subsequent one-year approval period. For example, if an IRB conducts initial review of a research project and recommends approval without conditions on October 1, 2009 for one year, the IRB may conduct its first continuing review anytime between September 1 and October 1, 2010, and recommends re-approval of the research for another one-year period that expires on October 1, 2011.

4.14.7 Managing protocols with lapsed approval. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date assigned by the IRB. DON HRPP recommends that the IRB and the investigator plan ahead to ensure that continuing review and re-approval of research occurs prior to the end of the approval period specified by the IRB. Continuing review of research by the IRB and re-approval by the IO should occur on or before the date of expiration of the approval. A lapse in institutional approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and the IO has re-approved the research by the expiration date of institutional approval. If a lapse occurs, intervention and interactions on current subjects may continue only when the IRB finds that an overriding safety concern or ethical issue is involved, and that it is in the best interests of individual subjects to continue participation. The IRB should address these situations on a case-by case basis.

4.14.7.1 Command process. Commands should maintain a process for tracking

research expirations and for notifying investigators of impending and actual expiration of approval. If the IO does not approve the research by the expiration date specified by the IRB, approval for the research is considered expired at 2400 on that date. The PI is responsible for obtaining command approval prior to continuing research.

4.14.7.2 Research activities. When institutional approval expires, regardless of the level of review, all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects must stop; unless it is determined to be in the best interests of already enrolled subjects to continue participating in the research. Enrollment of new subjects cannot occur after the expiration of institutional approval until continuing review by the IRB and approval by the IO has occurred. [32 CFR 219.109(a) and (e)].

4.14.7.3 IRB notification. If a study expires and enrolled subjects are undergoing study interventions, the PI should contact the IRB. (See 4.14.10b.)

4.14.8 Communicating the IRB's continuing review determination to the command and investigators. IRB continuing review recommendations should be communicated to the IO of the command holding the DON assurance.

4.14.8.1 Written IRB procedures related to continuing review should describe which office(s) and official(s) are notified of IRB findings and actions regarding continuing review and how notification is carried out.

4.14.8.2 Following action by the IO, the command/IRB must notify the investigator of the continuing review determinations. If the determination is to approve continuation of the research, the communication should indicate the date of approval, the expiration date or date of next review, and the review process. If the determination is to disapprove continuation, the communication must indicate the reason(s) for disapproval [32 CFR 219.109(a) and (e)]. Commands should follow a written procedure for communicating IRB findings and recommendations to the IO, documenting IO action, and communicating results to the PI.

4.14.9 Investigator Responsibilities for continuing review. The Investigator is responsible for:

- a. Obtaining command approval prior to continuing research;
- b. Fulfilling continuing review requirements in time for: The IRB to review the research; the PI to respond to the review (if necessary); the IRB to review any required modifications; and the IO to approve the continuation of research prior to the expiration date assigned by the IRB;
- c. Following command policies and procedures for continuing IRB review and command approval of research;

d. Submitting information and materials required by the IRB as outlined in Table IV; and

e. Knowing effective dates of institutional approval including the expiration date.

4.14.10 Investigator responsibilities for lapsed approvals. If the IRB has not conducted continuing review and the IO has not re-approved a research project by the expiration date, the PI must:

a. Stop all research activities involving human subjects, including subject recruitment and enrollment, data collection and data analysis, unless the IRB determines it to be in the best interest of already-enrolled subjects to continue participating;

b. Submit to the IRB a list of all participants for whom expiration could cause harm and seek confirmation that the IRB agrees that those subjects should be allowed to continue; and

c. Secure IRB review and command approval before restarting research activities.

4.14.11 Reporting to DON HRPP. All continuing review documents approved at the command level must be submitted to the DON HRPP as soon as they are available for headquarters-level administrative review [SECNAVINST 3900.39D, paragraph 8.c.(17)].

TABLE III. PROCEDURES FOR CONDUCTING CONTINUING REVIEW

A command must prepare and maintain – and the IRB must follow – written procedures for the continuing review of research [32 CFR 219.103(b)(4), 219.108(a), and 219.115(a)(6)]. These should address:

1. The procedures for informing investigators of their responsibilities regarding continuing review under 32 CFR 219;
2. The list of documents to be submitted by investigators for continuing review, the timeframe for submission of these documents to the primary reviewers and to all other IRB members, and the procedure for requesting these documents from the investigator;
3. Any primary reviewer system used;
4. Any process that may be used to supplement the IRB's continuing review;
5. For research requiring continuing review at a convened meeting, the timing of document distribution prior to IRB meetings;
6. Possible IRB actions to be taken on research projects undergoing continuing review;
7. Continuing review at convened meetings;
8. Continuing review under an expedited review procedure;
9. Communication of expedited approval actions to IRB members;
10. Communicating to investigators regarding continuing review of research;
11. Changes or clarifications required by the IRB, if any, as a condition of institutional approval;
12. Handling of investigators' responses to the IRB's requests for changes or clarifications;
13. Notification of the institutional office(s) and official(s) of IRB findings and actions regarding continuing review;
14. The effective date of institutional approval following continuing review;
15. Management of protocols with lapsed approvals;
16. Communication of the period of approval following continuing review to the investigator;
17. Identification of protocols requiring review more often than annually, including specific criteria used to make these determinations;
18. Projects needing verification from sources other than the investigators that no material changes have occurred since previous IRB review.

TABLE IV. DOCUMENTS TO SUBMIT FOR CONTINUING REVIEW

For projects undergoing continuing review, the IRB should require investigators to report:

1. Number of subjects enrolled (since last review, total enrolled, withdrawn, completed, still undergoing interventions, vulnerable populations, etc.);
2. Amendments approved by the command since the IRB's initial review or the last continuing review;
3. New and relevant information since the last IRB review, especially information about risks associated with the research;
4. Unanticipated problems and available information regarding adverse events;
5. Withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known;
6. Complaints about the research from subjects or others since the last IRB review;
7. A risk-benefit assessment based on study results and/or new information;
8. Significant events, milestones, problems, and unplanned delays;
9. Modifications made to the protocol, and an explanation for all deviations or variances from the protocol;
10. Subjects inappropriately enrolled in the research, for example, those who did not meet inclusion criteria or who met exclusion criteria but were enrolled anyway;
11. An accounting of all subjects who signed an informed consent document, including number who: completed participation; are still participating; or withdrew from the research and the reason for their withdrawal;
12. Internal or external audits;
13. The IRB-approved protocol and informed consent document(s) and any proposed modifications to the informed consent document or protocol;
14. For FDA-regulated research, the Investigator's Brochure, if available, including any modifications;
15. Other significant information related to subject risk, such as the most recent report from any Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) monitoring the research, if available.

4.15 IRB meeting minutes and records format and content. 32 CFR 219.115(a)(2) and 21 CFR 56.115(a)(2) require that "Minutes of IRB meetings shall be in sufficient detail to show attendance at the meeting; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution." IRB meeting minutes should enable a reader who was not present at the meeting to determine exactly how and why the IRB arrived at its decisions. They also should provide the IRB with sufficient detail to help it reconstruct its discussions later if necessary.

4.15.1 Minutes documentation. IRB meeting minutes should document the following:

- a. Attendance;
- b. Whether a quorum exists;
- c. Actions taken by the IRB;
- d. Separate deliberations for each action;
- e. Votes for each protocol as numbers for, against, abstaining, or recused. For example: "For: 7 Against: 3 Abstain: 0 Recused: 2;
- f. When an alternate member replaces a primary member;
- g. The basis for requiring changes in research;
- h. The basis for recommending disapproval of research;
- i. A written summary of the discussion of controverted issues and their resolution;
- j. Names of any IRB member(s) who leave the meeting due to a conflicting interest, and that the absence is caused by a conflicting interest;
- k. Time in/time out for anyone leaving the meeting;
- l. When a consultant is in attendance;
- m. For initial and continuing review, the approval period, including identification of research that warrants review more often than annually, and the reason for more frequent review;
- n. Level of risk determined by the convened IRB: minimal risk or more than minimal risk, with study-specific justification for the determination;

o. The justification for the recommendation of approval of research involving vulnerable populations, including but not limited to children, prisoners, pregnant women, fetuses, and/or neonates; and

p. Documentation of special protections for groups of subjects who are likely to be vulnerable to coercion or undue influence (e.g., active duty military, decisionally impaired, supervisor-subordinate).

4.15.2 Review of findings of UPIRTSOs, noncompliance, and suspensions/terminations of previously approved research. Documentation in the IRB minutes should include:

- a. Discussion and rationale for the action;
- b. Consideration of the rights and welfare of past or current study subjects;
- c. Terms of the corrective action plan and the timeline for completion; and
- d. The IRB vote on non-compliance (serious and/or continuing), unanticipated problems involving risk to subjects or others, and suspensions/terminations of previously approved research.

4.15.3 Review of regulatory requirements 32 CFR 219.111 and 21 CFR 56.111. DON HRPP recommends the IRB, in its meeting minutes, document that it considered all the regulatory review requirements. Documentation for each protocol should include, at a minimum, IRB determinations that:

- a. Risks are minimized and reasonable in relation to anticipated benefits;
- b. The selection of subjects is equitable;
- c. Informed consent is obtained and documented unless a waiver is granted;
- d. Measures to protect the privacy and confidentiality of data are adequate;
- e. Adequate provisions for monitoring data to ensure safety are made; and
- f. Appropriate safeguards for vulnerable populations are in place.

4.15.4 Protocol specific content. Some protocols will require special considerations in order to meet review criteria for approval. Documentation should reflect specific regulatory requirements and findings regarding matters including, but not limited to:

- a. Acknowledgment and management of conflicts of interest disclosed by study personnel;

- b. Need for permission of one or both parents for research involving children;
- c. Findings related to the involvement of pregnant women, fetuses or neonates, prisoners, and individuals with impaired consent capacity;
- d. Additional safeguards required for the involvement of other vulnerable subjects (including safeguards for military personnel);
- e. Significant risk/non-significant risk determinations for investigational devices;
- f. IND exemption criteria are met or the requirement for IND application;
- g. Consultants' statements;
- h. Waiver of documentation of informed consent (if applicable);
- i. Waiver of informed consent (if applicable); and
- k. Waiver of or alteration to HIPAA authorization (if applicable).

4.15.5 Availability of Minutes for Review. The IRB minutes should be distributed to attending IRB members for review and comment. The signed minutes should be reviewed and considered by the IO. The IRB minutes, once approved, may not be altered by anyone except by the IRB Chair with the concurrence and approval of the convened IRB (e.g., to correct factual or typographical errors). All approved minutes should be accessible for inspection and copying by authorized representatives of DON HRPP, OHRP, FDA, or other authorized entities at reasonable times and in a reasonable manner. All research protocols and supporting documentation, including IRB minutes shall be submitted to DON HRPP for Navy SG headquarters-level administrative review [SECNAVINST 3900.39D paragraph 8c].

4.16 Quorum requirements for review of research by the convened IRB. This guidance describes the requirements and process for review of human subject research via a convened IRB and applies to initial and continuing review of research proposals. It also applies to amendments to research proposals that are not exempt and that do not qualify for expedited review procedures.

4.16.1 Policies and procedures. 32 CFR 219.103(b)(4) and 21 CFR 56.108(a) require that commands have written IRB procedures for both initial and continuing review of research. Policies and procedures for convened meetings should require that:

- a. A majority of IRB members be present;
- b. At least one member whose primary concerns are in scientific areas and at

least one member whose primary concerns are in nonscientific areas be present;

c. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting;

d. If quorum is lost during a meeting, the IRB cannot take votes until the quorum is restored. If required members (e.g. non-scientific) leave the room and quorum is lost, votes cannot be taken until the quorum is restored, even if more than half the members are still present.

e. The individual who determines that a quorum of the IRB membership is present, and how it is documented;

f. The role of the Chair and Vice Chair prior to, during, and after the meeting is defined; including the Chair's voting responsibilities;

g. The expiration date calculated;

h. Per SECNAVINST 3900.39D, paragraph 6(b), IRB members and ad hoc participants (e.g., consultants) do not participate in any review in which they have a conflict of interest, except to provide information requested by the IRB. IRB members with a conflict are documented in the minutes as being absent with an indication that a conflict of interest was the reason for the absence. The definition of a conflict of interest requires consideration of both financial and non-financial interests of IRB members and ad hoc participants [SECNAVINST 3900.39D, paragraph 6b]. (See 4.5)

i. The attendance requirements for the non-affiliated member should be defined. Although 32 CFR 219.108(c) does not specifically require the presence of a member not otherwise affiliated with the command to constitute a quorum, DON HRPP considers the presence of such members an important element of the IRB's diversity. Per DoD Instruction 3216.02, enclosure 3, subparagraph 3a(7)(b), DON IRBs shall designate at least one alternate for the non-affiliated member. Although the presence of a non-affiliated member is not a requirement to have a quorum, the designation of one or more alternates will increase the likelihood that a non-affiliated member is present at the meetings. It is recommended that the non-affiliated member be present at no less than half of the IRB meetings in a calendar year.

4.16.2 Use of Teleconferencing for IRB Meetings. The Department of Defense (DoD) regulations [32 CFR 219.108(b)], "the Common Rule," require IRBs to "review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas." There are limited situations in which IRB members may participate in IRB meetings via teleconference, or video conference.

4.16.2.1 When IRB members participate via teleconference/videoconference, meeting minutes should document that each member received all pertinent material prior to the meeting and can equally and actively participate in the discussion.

4.16.3 Acceptable practices for IRB meetings. DON HRPP recommends that IRB meetings take place with all participating members physically present, however in circumstances where not all IRB members can convene in the same physical location, DON HRPP will recognize as "convened" those IRB meetings conducted, in whole or in part, via video teleconference or telephone conference call, so long as:

- a. Each participating IRB member has received all the relevant materials with sufficient time for review prior to the meeting;
- b. Each participating IRB member is able to participate actively in the real-time discussion of the relevant protocols; and,
- c. All usual requirements, such as those regarding quorum and membership, are met.

4.16.4 Ad hoc consultants. IRBs may invite individuals as consultants to provide expertise to assist the IRB in its review, and these individuals may participate via video-conference or teleconference. These individuals may not vote per 32 CFR 219.107(f).

4.16.5 Documentation of video or teleconferencing. In situations where video-conferencing or teleconferencing are used the IRB meeting minutes should document:

- a. Which members attended via these methods and for which portions of the meeting;
- b. That such members received all relevant materials with sufficient time for review prior to the meeting;
- c. Whether the members participating via video-conferencing or teleconferencing were able to participate actively in the real-time discussions; and
- d. The rationale for why such members were unable to attend in person.

4.17 The development and implementation of command monitoring plans. To ensure the protection of human subjects and adherence to DoD/DON regulations and instructions DON commands should develop and implement a plan to monitor human subjects research. SECNAVINST 3900.39D paragraph 6a(4)(b) states that one of the key requirements of the DON assurance is a command's plan for monitoring its human research. The purpose of a monitoring plan is to ensure protection of human subjects, adherence to approved protocol, and compliance with DoD/DON regulations and instructions.

4.17.1 Monitoring plan based on command characteristics. DON commands should consider specific command characteristics when developing a command monitoring plan, including:

- a. The volume and attributes of the research taking place at command;
- b. Risks involved in research taking place at command;
- c. Resources that the command has available to carry out a command monitoring plan, and how to best protect human subjects and fulfill regulatory responsibilities with resources available;
- d. Common problems occurring at the command.

4.17.2 Monitoring plan focus. Commands should focus their monitoring efforts and define specifically how monitoring will be carried out, what documents and processes will be monitored, and how often monitoring will be carried out.

4.17.3 Investigator-level monitoring. A command monitoring plan should include monitoring at the investigator level. Investigator-level monitoring may include a plan to monitor a certain percentage of protocols, a time period in which that percentage of protocols will be monitored, the processes that will be monitored, and/or a list of investigator files that will be monitored. Common investigator-level targets include:

- a. Adherence to protocol – subject eligibility, correct procedures, medications/treatments (doses, strengths), recruitment, advertisements, consent document, consent process, added protections for vulnerable populations;
- b. Unanticipated problems;
- c. Conflicts of interest (investigators);
- d. Confidentiality of records;
- e. Completeness of investigator files;
- f. Subject/family complaints; and
- g. Scientific review.

4.17.4 IRB-level monitoring. A command monitoring plan should include monitoring at the IRB level. IRB-level monitoring may include a plan to monitor a specific percentage of IRB records/minutes, the timeframe in which the records/minutes will be monitored, and/or the expedited/convened IRB review process. Common IRB-level targets include:

- a. Investigator records;
- b. IRB minutes;

- c. Composition/expertise of IRB;
- d. Quorum requirements;
- e. Initial and on-going training; and
- f. Conflict of interest (IRB members).

4.17.5 HRPP-level monitoring. A command monitoring plan should include monitoring at the HRPP level. HRPP-level monitoring may include a plan to review specific aspects of the overall command HRPP. Common IRB-level targets include:

- a. Quality of education and training of staff involved in research;
- b. Communication between departments or components of command HRPP;
- c. Whether appropriate resources allocated to support HRPP;
- d. Appropriate efficiency of HRPP processes; and
- e. HRPP policies and procedures.

4.17.6 Addressing and reporting non-compliance. DON commands should develop policies and procedures for reviewing, addressing, and reporting non-compliance when found. According to SECNAVINST 3900.39D, DON command IRBs and IOs must review all allegations of non-compliance with human subject protections and take action if appropriate. DON commands must report the initiation of all investigations of non-compliance and the results to DON HRPP and appropriate sponsors, regardless of findings [SECNAVINST 3900.39D, paragraph 8.c.(23)].

4.17.7 Monitoring and education. It is recommended that DON commands develop education and training opportunities related to the problems found while monitoring internal processes with the purpose of improving the protection of human subjects and compliance, over time.

4.18 The use of the Institutional Agreement for IRB Review (IAIR), the Individual Investigator Agreement (IIA), and the Department of Defense (DoD) DON Addendum to the Federalwide Assurance. Any institution engaged in non-exempt research involving human subjects that is conducted or supported by the Department of Defense (DoD) shall have a Federal assurance consistent with 32 CFR 219.103 and acceptable to the funding agency. Non-DoD institutions should also obtain a DoD-DON Addendum to their Federalwide assurance (see 4.19.2). Human subject research shall not be initiated until the institution holds a valid assurance for the Protection of Human Research Subjects, and the research protocol has been reviewed by an IRB and approved by an appropriate research approval authority. Researchers may rely on

IRBs outside their own institution. This may be accomplished via the IAIR or IIA process. Current templates can be found at the [DON HRPP Website](#).

4.18.1 Engaged vs. supported. An institution is engaged in research involving human subjects when its personnel are conducting activities covered by 32 CFR 219.101 and DoD Instruction 3216.02. An institution whose personnel are doing only one of the following is *supporting* the research and might not be *engaged* in the research: funding, providing equipment, providing access to or information about potential human subjects (but not recruiting human subjects), providing data or specimens (either identifiable or not), or overseeing the research from a regulatory or compliance standpoint.

4.18.2 Institutional Agreement for Institutional Review Board Review (IAIR). An IAIR allows an institution that will be engaged in human subjects research (HSR) to rely on an IRB that is not organizationally or legally part of the institution. The IAIR can apply to a single DoD-conducted or -supported research protocol only; a group of DoD-conducted or supported research protocols; or, all DoD-conducted or -supported research performed by the institution.

a. Institutions should ensure the reviewing IRB has the appropriate expertise for the type of research requiring review.

b. The institution conducting the research remains responsible for monitoring and overseeing the DoD-conducted or supported research from its inception to conclusion.

c. DON commands may rely on a non-DoD IRB if the:

(1) Collaborating non-DoD institution has an appropriate Federal assurance;

(2) DON command's IRB and non-DoD institution's IRB have a signed IAIR that has been endorsed by the DON HRPP; and

(3) Involvement of DON personnel in the conduct of the HSR is secondary to that of the non-DoD institution.

(4) DON HRPP has conducted an appropriate administrative review of the HSR to ensure compliance with DoD policies and procedures prior to the command's engagement in the research.

d. An IAIR is not needed if each institution engaged in the research complete independent IRB reviews (DoD Instruction 3216.02 requires that duplicative IRB reviews be justified).

e. Institutions will maintain all documents supporting the DoD Institutional Agreement for IRB Review. These documents will be available for review by the Surgeon General of the Navy, DON HRPP, and the institutions named in the agreement per

SECNAVINST 3900.39D, paragraph 8c (20).

4.18.3 Individual Investigator Agreement (IIA). If a researcher is not associated with an institution that holds a Federal assurance, the researcher may use an IIA to associate with an institution that does hold a Federal assurance to fulfill the requirement of conducting non-exempt research involving human subjects under an approved Federal assurance.

- a. An IIA allows an individual researcher who is engaged in HSR and not an employee of the assured institution, to be associated with the assured institution in order to conduct research.
- b. The IIA describes the responsibilities of the assured institution.
- c. The IIA, when signed, becomes part of the assured institution's Federal assurance for the Protection of Human Research Subjects approved by DoD [and may become part of the Federalwide Assurance (FWA) approved by the Department of Health and Human Services (DHHS)].
- d. The IIA may apply to all research performed by the investigator in collaboration with the institution with the assurance, or may be applicable only to the research identified in the scope of the IIA.
- e. IIAs may be used to cover individuals conducting HSR at DON commands that do not have their own assurance. A DON-assured command may agree to cover outside individuals (DoD civilian employees and members of the Services) under their assurance even if the command is not conducting the research.
- f. Contractors providing support services to the government by working on HSR projects at DON commands whose organization does not have a FWA and DoD-DON Addendum may be covered under the DON command assurances via the IIA.
- g. Individuals that are party to the IIA must not engage in HSR until the IRB has reviewed and recommended approval, the assured command has approved the research, the IIA is signed by all parties, and the investigator receives a fully-signed and endorsed copy of the agreement from the DON HRPP. Individuals should be aware that there may still be additional requirements of their employer that must be followed.

4.19 DoD/DON requirements imposed for DoD-supported research involving human subjects. DoD Instruction 3216.02 defines DoD-supported as research involving human subjects for which the DoD is providing at least some of the resources. Resources may include but are not limited to funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by non-DoD institutions (extramural research).

4.19.1 Application of DoD/DON-supported research. The definition of DoD-supported research may be applicable in a number of research scenarios in which DoD is providing resources. Two basic categories are:

4.19.1.1 Research conducted by a non-DoD institution supported by a contract mechanism. The research must comply with Defense Federal Acquisition Regulation Supplement (DFARS) section 252.235-7004 of title 48, CFR and DoD Instruction 3216.02, enclosure 3, section 4.

4.19.1.2 Research conducted by a non-DoD institution supported by other formal agreements not subject to section 252.235-7004 of title 48, CFR, including grants, assistance agreements, and cooperative research and development agreements. The research must comply with the applicable requirements of DoD Instruction 3216.02. The requirements applicable to Human Research Protection Official (HRPO) review as specified in section 252.235-7004 of title 48, CFR and DoD Instruction 3216.02 also will apply to the oversight of other formal agreements.

4.19.2 DoD-DON Addendum to the FWA. Non-DoD institutions should obtain the DoD-DON Addendum to their FWA. The Addendum identifies the unique DoD and DON requirements that are not specifically included in the institution's FWA. When DON commands are collaborating with non-DoD Institutions supported by the DON for research involving human subjects, the DON command should verify that the institution holds a valid DoD Addendum.