



DEPARTMENT OF THE NAVY
OFFICE OF THE SECRETARY
1000 NAVY PENTAGON
WASHINGTON, D.C. 20350-1000

SECNAVINST 3900.39E CH-1
ONR 343
29 MAY 2018

SECNAV INSTRUCTION 3900.39E CHANGE TRANSMITTAL 1

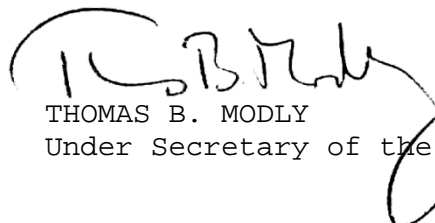
From: Secretary of the Navy

Subj: HUMAN RESEARCH PROTECTION PROGRAM

Encl: (1) Revised Page 1
(2) Revised Page 5
(3) Revised Enclosure 3, Pages 1 and 2
(4) Revised Enclosure 3, Pages 4
(5) Revised Enclosure 3, Pages 6 through 10
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(7) Revised Enclosure 3, Pages 16 through 18
(8) Revised Enclosure 4, Pages 1 through 3
(9) Revised Enclosure 4, Page 5
(10) Revised Enclosure 4, Pages 7 through 9
(11) Revised Enclosure 4, Page 11
(12) Revised Enclosure 5, Pages 1 through 9

1. Purpose. This change transmittal is issued to clarify language in pages 1 and 5 of the basic instruction and enclosures (3) through (5). The updated language clarifies the Department of the Navy obligation to comply with Department of Defense requirements for this program. Minor formatting changes were made throughout the change transmittal.

2. Action. Remove the pages identified in the basic instruction and replace with the pages of this change transmittal as noted in enclosures (1) through (12).


THOMAS B. MODLY
Under Secretary of the Navy

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From: Secretary of the Navy

Subj: HUMAN RESEARCH PROTECTION PROGRAM

Encl: (1) Changes
(2) References
(3) Responsibilities
(4) Procedures
(5) Definitions
(6) Reports Control

1. Purpose. To establish policy and assign responsibility for the protection of human subjects in research conducted or supported by the Department of the Navy (DON) per Department of Defense (DoD) Instruction 3216.02, reference (a) and to implement reference (b) also known and hereinafter referred to as "the Common Rule", also subparts B through D of part 46 of Title 45, Code of Federal Regulations, reference (c) as implemented by reference (a). This instruction seeks to harmonize DON policy and procedures with those of the other Services and DoD Components. This instruction has been extensively rewritten and should be read in its entirety.

2. Cancellation. SECNAVINST 3900.39D

3. Background. DoD policy and procedures, reference (a), have been expanded significantly. This instruction must be read together with reference (a). Significant changes are listed in enclosure (1), References in enclosure (2), Responsibilities in enclosure (3), Procedures in enclosure (4), and Definitions in enclosure (5).

4. Applicability

a. This instruction applies to:

(1) All DON-conducted or -supported research involving human subjects as defined in enclosure (5) and discussed below. All such activities must include both systematic investigation designed to develop or contribute to generalizable knowledge and involve a living individual about whom an investigator

conducting research obtains data through intervention or interaction with the individual or about whom identifiable private information is obtained. All activities meeting both of these conditions will hereinafter be referred to as "research involving human subjects" in this instruction.

(2) Activities such as Research, Development, Testing, and Evaluation (RDT&E) that meet the definition of research involving human subjects, as defined in enclosure (5), as well as clinical investigations or medical activities regulated by the Food and Drug Administration (FDA) per reference (d).

(3) Activities including social-behavioral, educational, and human factors research that meet the definition of research involving human subjects, as defined in enclosure (5).

(4) Applicability is not dependent upon the budget activities funding the research, the mission of the DON organization conducting or supporting the research, the security classification of the research, the location of the research in the United States or a foreign country, or whether the research is conducted or supported under a program that is not considered research for other purposes.

b. This instruction does not apply to certain activities. See the definitions of "research involving human subjects" and "DON-supported research" at enclosure (5). The following activities conducted or supported by the DON are NOT research involving human subjects:

(1) Activities 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 DON, including health surveillance per reference (e) and the use of medical products per reference (f).

(2) Authorized health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment.

(3) Activities performed for the sole purpose of medical quality assurance per references (g) and (h).

(4) Activities performed solely for an Operational Test & Evaluation (OT&E) project where the activities and project(s) meet the definition of OT&E per reference (i).

(5) Activities performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, 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.

(6) Activities including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, student end-of-course critiques, 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.

(7) Survey, interview, or surveillance activities and related analysis performed solely for authorized foreign intelligence collection purposes per reference (j).

(8) Research using cadavers. However, institutions proposing to support or conduct this research shall meet requirements for scientific merit, comply with applicable State and local laws regulating organ donation for science or research, and verify that the research is limited to cadavers.

5. Definitions. See enclosure (5).

6. Policy. It is DON policy that:

a. All research involving human subjects that is conducted or supported by DON shall comply with reference (b), which incorporates the ethical principles of respect for persons, beneficence, and justice, as described in the principles of the Belmont Report; Volume 44 of the Federal Register page 23192.

b. Certain categories of human subjects in research are recognized as vulnerable populations, groups, or individuals and are afforded additional protections as specified in paragraph 7 of enclosure (4) of this instruction.

c. Research involving human subjects for testing of chemical or biological warfare agents is generally prohibited per reference (k), subject to possible exceptions for research for prophylactic, protective, or other peaceful purposes.

d. DoD-appropriated funds shall not be used to support research involving a human being as an experimental subject, as defined in this instruction; without the prior informed consent of the experimental subject or per reference (l) and paragraph 9 of enclosure (4) of this instruction. The definitions of research involving a human being as an experimental subject and research involving human subjects are different; see enclosure (5) of this instruction.

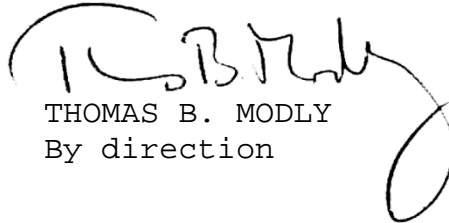
e. Research involving human subjects covered under this instruction shall also comply with applicable Federal and State laws and regulations. When the research is conducted outside of the United States, it must also comply with applicable requirements of the foreign country and its national laws and requirements. In the event of an unresolved conflict between this instruction, including its references and other applicable laws and requirements, such that compliance with both is impossible, the requirements most protective of the human subjects shall be followed. When there is an unresolved conflict, DON institutions shall consult with their legal counsel and coordinate with the Director, DON Human Research Protection Program (HRPP) to seek guidance from the Assistant Secretary of Defense for Research and Engineering (ASD(R&E)).

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

"Food, Drug, and Cosmetic Act," 21 U.S.C. 321 (ff), the "Dietary Supplement Health and Education Act of 1994," Public Law 103-417 and the "FDA Food Safety Modernization Act," Public Law 111-353, is based on the intent of the clinical investigation. If a clinical investigation is intended to evaluate the dietary supplements' (e.g., vitamins, minerals, amino acids, botanicals, etc.) or over-the-counter drugs' ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required per reference (d), unless the FDA determines otherwise. When it is uncertain whether an IND is required, it is recommended that the Principal Investigator contact the appropriate review division in the appropriate FDA Center for advice.

7. Records Management. Records created as a result of this instruction, regardless of media and format, shall be managed, per reference (m).

8. Reports. See enclosure (6) for reporting requirements contained within this instruction.



THOMAS B. MODLY
By direction

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CHANGES

1. This instruction incorporates significant changes including the following:

a. Assigns to the Under Secretary of the Navy (UNSECNAV) new reporting requirements of the Assistant Secretary of Defense (Research & Engineering) (ASD(R&E)).

b. Assigns additional responsibilities to the Navy Surgeon General (SG) for review and approval of waivers to the Department of the Navy (DON) policy regarding human research protection.

c. Identifies responsibilities for the Special Assistant to the Surgeon General of the Navy for Human Research Protections (SAHRP).

d. Assigns responsibilities to the Director, DON Human Research Protection Program.

e. Includes Human Research Protection Official (HRPO) review process for DON-supported research involving human subjects conducted by non-Department of Defense institutions.

f. Assigns additional responsibilities to the DON's Institutional Review Boards (IRBs) for approval of research.

g. Includes responsibilities and the review process for Exemption Determination Officials (EDOs).

REFERENCES

- (a) DoD Instruction 3216.02 of 8 November 2011
- (b) 32 CFR 219
- (c) 45 CFR 46, Subparts B-D
- (d) 21 CFR 50, 56, 312, 600, 812
- (e) 10 U.S.C. 1074f
- (f) DoD Instruction 6200.02 of 27 February 2008
- (g) 10 U.S.C. 1102
- (h) DoD Instruction 6025.13 of 17 February 2011
- (i) 10 U.S.C. 139(a)(2)(A)
- (j) DoD Directive 5240.01 of 27 August 2007
- (k) 50 U.S.C. 1520a
- (l) 10 U.S.C. 980
- (m) SECNAV M-5210.1 Department of the Navy Records Management Program Records Management Manual of 7 November 2007
- (n) 42 U.S.C. 289g-289g-2
- (o) Public Law 107-347, "Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA)," 17 Dec 02
- (p) 72 FR 33362-33377
- (q) Marine Corps Order 3900.18 of 21 Jan 11
- (r) 48 CFR 207.172, 235.072(e), and 252.235-7004
- (s) Minimum Education Requirements for Department of Defense Personnel Involved in Human Research Protection of 16 Aug 2012
- (t) 32 CFR 108
- (u) 32 CFR 728.77
- (v) E.O. 13526
- (w) 44 U.S.C. 3501

RESPONSIBILITIES

1. The Secretary of the Navy (SECNAV) shall:

a. Establish and properly resource the Department of the Navy (DON) Human Research Protection Program (HRPP) to ensure the protection and welfare of human subjects in research supported by the DON.

b. Request from the Assistant Secretary of Defense (Research & Engineering) (ASD(R&E)) the authority to waive the requirements for informed consent to conduct research involving use of humans as experimental subjects and, if delegated authority, approve protocols requesting a waiver of informed consent, per reference (l). This also includes approval of protocols involving exceptions from informed consent requirements for emergency research per section 50.24 of reference (d).

2. The Under Secretary of the Navy (UNSECNAV) shall:

a. Serve as the approval authority for research involving:

(1) Inherently controversial topics, such as those likely to attract significant media coverage or that may invite challenge from interest groups;

(2) Waivers identified per reference (a) with the exception of authorities retained by SECNAV, paragraph 1 of this enclosure and waivers approved by the Navy Surgeon General (SG), per paragraph 4q of this enclosure, and by the Institutional Official (IO) per paragraph 9d(13) of this enclosure.

b. Forward to ASD(R&E):

(1) All proposed research, to include a copy of all reports provided to the appropriate Congressional Committees per reference (k), involving human subjects for testing of chemical or biological warfare agents.

(2) Copies of any waivers from requirements that have been granted per reference (a).

(3) Copies of any approved fetal research per reference (n).

(4) Copies of any research involving human subjects conducted, per reference (o). Also send a copy to the Office of Management and Budget (OMB) per reference (o) and pages 33362-33377 of Volume 72 of reference (p).

(5) Classified research involving human subjects that must be submitted for approval to the Secretary of Defense (SECDEF).

(6) Research requiring exercise of authorities of the Head of Department per references (b) and (c) as implemented per reference (a) for research described in paragraph 7 of enclosure (4) of this instruction.

(7) Research requiring a grant of exception to reference (a).

3. The Assistant Secretary of the Navy for Research, Development and Acquisition (ASN(RD&A)) shall utilize the Deputy Assistant Secretary of the Navy for Research, Development, Test & Evaluation (DASN RDT&E) to monitor:

a. All research and reports forwarded to UNSECNAV, SECNAV, ASD(R&E) and SECDEF.

b. Any allegation of serious or continuing noncompliance related to research involving human subjects that has been substantiated by inquiry or investigation and any subsequent actions taken based on the findings per reference (a), enclosure (3), section 16.

c. Any reports to ASD(R&E) of notifications to a DON institution by another federal agency or by an appropriate State agency or foreign government that the institution is under investigation for cause or for noncompliance with the applicable laws and regulations, including the Common Rule.

d. Any Substantiated Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO).

e. Any suspension or termination of Institutional Review Board (IRB) approval.

4. The Surgeon General of the Navy (Navy SG) shall:

a. Have authority and responsibility for the DON HRPP with the exception of authorities retained by SECNAV and UNSECNAV. Establish and oversee DON policies and procedures for the protection of human subjects in research that ensure compliance with Federal, DoD, and DON requirements.

b. Ensure the DON HRPP Management Plan identifies the single, senior official having the authority and responsibility for implementing the management plan and identifies all authorities delegated by SECNAV. Approve the DON HRPP Management Plan or delegate this approval authority to the Special Assistant to the Surgeon General of the Navy for Human Research Protections (SAHRP).

c. Establish, maintain, and properly resource a headquarters DON HRPP oversight office.

d. Be responsible for approval and oversight of assurances to DON institutions.

e. Oversee each DON IO's implementation of their institution's HRPP.

f. Appoint and provide members to intra- and inter-agency committees and to the DoD Coordinating Committee for Human Research Protection Programs (CCHRPP) when requested by the ASD(R&E) per reference (a), enclosure (3), section 18.

g. Provide in a timely manner to the UNSECNAV (with a copy to ASN(RD&A)) the submissions identified at paragraph 2 of this enclosure.

h. Forward protocols identified at paragraph 1 and 2 of this enclosure for approval to SECNAV and UNSECNAV with a copy to ASN(RD&A), along with recommendations.

i. Restrict DoD-DON Assurances and protocols including suspension and termination.

j. Provide concurrence, as appropriate, with any research involving human subjects conducted per reference (o) and forward copies of research to UNSECNAV for forwarding to ASD(R&E) per paragraph 2b of this enclosure.

k. Forward to ASD(R&E), with a copy to ASN(RD&A), any allegation of serious or continuing non-compliance related to research involving human subjects that has been substantiated by inquiry or investigation and any subsequent actions taken.

l. Forward to ASD(R&E), with a copy to ASN(RD&A), any notifications to a DoD Component by another federal agency or by an appropriate State agency or foreign government that an institution of the Component is under investigation for cause or for non-compliance with the applicable laws and regulations, including the Common Rule.

m. Forward to ASD(R&E), with a copy to ASN(RD&A), any UPIRTSO related to research involving human subjects that has been substantiated by inquiry or investigation and any subsequent actions taken based on the findings.

n. Forward to ASD(R&E), with a copy to ASN(RD&A), any suspension or termination of IRB approval.

o. Review and process, and if appropriate, forward research and requests for waiver to the UNSECNAV per paragraph 2a of this enclosure for review and approval. Research requiring UNSECNAV approval under paragraph 2a(1) of this enclosure also shall be coordinated with DON Chief of Information (CHINFO) per SECNAVINST 5720.44C.

p. Review and approve, if appropriate, activities per reference (a), enclosure (3), section 7c(2).

q. Review and approve, if appropriate, waivers to the DON policy regarding human research protection.

r. May serve as the sponsor for Investigational New Drug (IND) applications and Investigational Device Exemptions (IDEs).

5. The Chief of Naval Research (CNR) shall provide support and expertise to the Navy SG and to DON HRPP for human research protection in research conducted or supported by the Navy and Marine Corps Systems Commands and institutions, operational forces, training Commands and DON-supported research involving human subjects performed by non-DoD institutions. CNR, through the Office of Naval Research, Research Protections Division, shall support:

- a. Periodic site inspections and assist visits and "for cause" investigations when necessary.
- b. Assignment of DON representatives to interagency, joint, and Service-level working groups as needed.
- c. Reviews of research by Navy and Marine Corps Commands and institutions involving human subjects.
- d. Development of DON HRPP policy and guidance.

6. Commandant of the Marine Corps (CMC) shall:

- a. Establish and maintain an HRPP within the Marine Corps, including meeting periodically with Marine Corps HRPP leadership.
- b. Issue and update, as required, per reference (q) to implement DON Human Research Protection requirements in the Marine Corps.

7. The Special Assistant to the Surgeon General of the Navy for Human Research Protections (SAHRP) shall:

- a. Serve as principal adviser to the Navy SG for Human Research Protection.
- b. Serve as a DON liaison to the ASD(R&E) and other federal agencies regarding Human Research Protection, including participation in inter- and intra-agency working groups, per direction of the Navy SG.
- c. Provide input to the Navy SG regarding DON membership in inter- and intra-agency working groups.
- d. Review and approve the DON HRPP Management Plan if approval authority is delegated by the Navy SG.

8. The Director, Department of the Navy, Human Research Protection Program (DON HRPP) shall:

- a. Provide subject matter expertise and guidance on all DON-supported research involving human subjects.

b. Manage the implementation, operation, and execution of the HRPP.

c. Review Individual Investigator Agreements (IIAs) and Institutional Agreements for IRB Review (IAIRs) involving DoD-DON Assurances during assist visits and site inspections.

d. Review and approve Command reliance on outside (external to the Command) Exemption Determination Officials (EDOs).

e. Establish a process for administrative review of DON-conducted research identified per reference (a), enclosure (3), section 3b.

f. Have authority to temporarily suspend DON-conducted research involving human subjects pending further investigation or audit.

g. Issue routine guidance and procedures (e.g., handbooks, templates, and Standard Operating Procedures (SOPs)). May draft and forward policy to Navy SG for approval via SAHRP.

h. Implement a quality assurance review program at DON HRPP Headquarters and DON institutions, including assist visits as necessary and periodic site inspections.

i. Support and oversee DON institutions in the establishment and operation of HRPPs, including obtaining assurances for performance of non-exempt research involving human subjects and establishment of IRBs.

j. Establish initial and ongoing training and education for DON personnel commensurate with their roles in research involving human subjects and issue training guidance.

k. Prepare submissions of reports for forwarding to higher-level officials within the DoD and DON.

l. Review and address the findings of investigations of allegations of non-compliance.

m. Ensure that allegations of UPIRTSOs, serious or continuing non-compliance and serious adverse events are appropriately investigated, substantiated and addressed by the institution and appropriately reported as required.

n. Participate, as appropriate, in review of allegations of research misconduct related to research involving human subjects and report to SAHRP. See enclosure (5) for the definition of research misconduct.

o. Review and accept DON institutions' proposed corrective action plans to address deficiencies in their HRPPs.

p. Coordinate with DON institutions in the processing and forwarding of protocol packages that require higher-level approval.

q. Maintain records regarding management of the DON HRPP.

r. Manage processing of waivers of the DON requirements and those stipulated per reference (a).

s. Provide headquarters-level administrative review and staffing of protocols requiring review and approval by higher authority (e.g., Navy SG, UNSECNAV, SECNAV, ASD(R&E) and SECDEF).

t. Act on behalf of the Navy SG to accept other Federal assurances.

u. Provide a briefing periodically regarding the DON HRPP to the Navy SG, CNR, and SAHRP.

v. When research is conducted outside the United States, in the event of unresolved conflicts between this instruction, including its references and other applicable laws and requirements, consult with legal counsel and seek guidance from ASD(R&E).

w. Review and accept DON institution's policies and procedures regarding the identification, training, and designation of EDOs and Human Research Protection Officials (HRPOs).

x. Ensure that the DON HRPP Management Plan identifies all authorities delegated by SECNAV and addresses each requirement per reference (a), enclosure 3, section 1.

y. Establish a process for administrative review of DON-conducted research or DON-supported research conducted by non-

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DoD institutions identified per reference (a), enclosure (3), section 7b(3).

z. Execute the responsibilities identified in paragraphs 4(k)through(n) of this enclosure if this authority is delegated by the Navy SG.

9. The Institutional Official (IO):

a. Must be senior military or a DON civilian official with the authority to commit the institution to comply with Federal, DoD and DON requirements. The IO heads the institution's HRPP and frequently serves as the Commander, Commanding Officer, Officer-in-Charge or other Senior Official at an institution.

b. In coordination with the Director, DON HRPP, establishes and maintains an HRPP to ensure the institution's compliance with this instruction.

c. The IO shall:

(1) Complete and document initial education and training prior to taking any HRPP-related action and comply with requirements for continuing education and training. See paragraph 5 of enclosure (4).

(a) Ensure initial and continuing education and training for all personnel involved in the conduct, review or approval of research involving human subjects, commensurate with their roles. See paragraph 5 of enclosure (4).

(b) Ensure any individual designated to make a determination (e.g., HRPO, IRB Chair, EDO) regarding research or exempt status does so in accordance with procedures codified in the institution's HRPP. See enclosure (5) for definitions of EDO and HRPO.

1. The individuals identified above with the authority to make these determinations must have appropriate training or experience. See paragraph 5 of enclosure (4). For EDOs, also see paragraph 3a of enclosure (4).

2. The individuals may be DON personnel assigned to the institution or personnel of another DoD

institution, if the IOs of both institutions agree to the arrangement with approval of the Director, DON HRPP.

3. More than one person can be designated to fulfill the roles of EDO and HRPO.

4. Ensure submission of updated documentation, including HRPO and EDO appointment letters, to Director, DON HRPP and when there are significant changes to the institution's policies or when there is a change in the IRB Chair.

(2) Provide the resources needed to ensure compliance with this instruction.

(3) Evaluate and improve the institution's HRPP annually.

(4) Establish and maintain policies and procedures to provide adequate oversight, including authority to suspend or terminate research involving human subjects.

(5) Ensure the establishment of a system to maintain research files, HRPP correspondence, IRB records and HRPP-related determinations (e.g., HRPO, EDO) as "project case files." See paragraph 15 of enclosure (4).

d. The IO of any DON institution Engaged in Conduct of Non-Exempt Research, in addition to the responsibilities described at paragraph 9c of this enclosure, shall:

(1) Establish and maintain a DoD-DON Assurance and other federal assurances, if appropriate.

(2) Submit new and renewal assurance documentation to the Director, DON HRPP for processing in accordance with paragraph 2a of enclosure (4).

(3) Identify on the institution's DoD-DON Assurance all IRBs that are part of their institution, or any IRBs not part of their institution that the institution will use to review research.

(4) For IRBs established by the institution:

(a) Approve IRB membership.

(b) Require the IRB to initiate investigations of allegations of serious or continuing non-compliance, serious adverse events, and UPIRTSOs, and promptly submit a notification to the IO and the Director, DON HRPP. Also provide notification regarding other items listed at paragraph 9d(10)(a)through(g) of this enclosure.

(5) Provide for policies, procedures and training to reduce the number of IRB and administrative reviews of collaborative research among DoD institutions. Duplicative reviews shall not be conducted without written justification to the Director, DON HRPP. See paragraph 1a and 1b of enclosure (4). The written justification is provided to ensure the Director, DON HRPP's situational awareness.

(6) Confirm that a scientific review process is established for non-exempt research involving human subjects conducted by the institution and the findings of scientific review are considered by the IRB.

(7) Review and forward to the Director, DON HRPP research which may require higher-level approval or waivers (by UNSECNAV, SECNAV, ASD(R&E) or SECDEF) before the research may begin.

(8) Establish procedures for review and approval of research by the IO before the institution becomes engaged in non-exempt research involving human subjects. The purpose of this review is to determine, on behalf of the institution and in light of DON requirements and local mission considerations, whether to permit the research. This review can be done before or after IRB approval and is not part of the IRB review process.

(9) Not allow research to be conducted that has been disapproved by the reviewing IRB.

(10) Upon completion of investigations required under this instruction, submit reports to Director, DON HRPP within 15 business days (including supporting documentation, information, review, disposition, recommendations and associated plans for corrective action) for the following:

(a) All investigations and audits of the institution's HRPP, including those conducted by outside

organizations (e.g., Food & Drug Administration (FDA) or Office of Human Research Protections (OHRP)).

(b) UPIRTSOs and serious adverse events.

(c) Investigations of serious or continuing non-compliance.

(d) Investigations of research misconduct.

(e) Suspensions and terminations of previously approved research.

(f) Significant communications between the institution and other federal departments or agencies, state agencies, or foreign governments regarding compliance and oversight.

(g) Copies of reports or submissions to the FDA required by reference (d).

(11) Ensure submission of all approvals for non-exempt research involving human subjects with supporting documentation (e.g., research protocols, minutes, command-generated checklist, IAIR, IIA, etc.) to Director, DON HRPP for headquarters-level administrative review.

(12) The IO, who is also a Commander or Commanding Officer, may serve, when appropriate, as the sponsor for IND applications (see reference (d), section 312) and IDEs (see reference (d), section 812). Other IOs considering sponsorship of an IND or an IDE, should coordinate with Director, DON HRPP. See paragraph 6f of this instruction.

(13) Review and approve if appropriate, requests for waivers submitted per reference (a), enclosure (3), section 10c(3).

e. The IO of any DON institution Engaged in Conduct of Exempt Research, in addition to the responsibilities described at paragraph 9c of this enclosure, shall:

(1) Ensure submission of exemption determinations with supporting documentation (e.g., research protocols, test plans,

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proposals, etc.) to Director, DON HRPP for headquarters-level administrative review.

(2) Retain the authority to impose additional review requirements for exempt research (e.g., scientific review, etc.).

f. The IO of any DON institution that supports non-DoD conducted research involving human subjects, in addition to paragraph 9c of this enclosure, shall:

(1) Disseminate information about requirements for review of non-DoD conducted research and establish a process to meet requirements per reference (a), enclosure (3), section 4 and ensure such requirements are addressed as part of the acquisition planning process per reference (r).

(2) When the institution awards contracts, grants, assistance agreements, and/or Cooperative Research and Development Agreements (CRADAs) for research involving human subjects, establish a formal procedure for Human Research Protection Official (HRPO) review, including coordination with Contracting or Grant Officer or Office of Research, Technology and Applications (ORTA) or other staff involved in coordinating agreements to ensure that appropriate information is included in solicitations, awards and agreements.

(3) When a DON institution provides support to non-DoD institutions for research that is not covered by a contract, grant, assistance agreement and/or CRADA, ensure coordination with Director, DON HRPP. In this context such support does not include research performed by DoD personnel. This typically occurs when non-DoD institutions request access to a facility or installation of a DON institution for the purpose of recruiting DON personnel or use of equipment for research (for other examples, see enclosure (5) for definition of DON-supported research involving human subjects).

(4) Ensure allegations of non-compliance with this instruction or reference (a) are properly investigated and reported to Director, DON HRPP.

10. The Human Research Protection Official (HRPO) shall be a Federal employee or Service Member designated by the institution's IO to review proposed effort(s). The HRPO shall:

a. Conduct timely review of documentation submitted by non-DoD institutions in accordance with the terms of Defense Federal Acquisition Regulation Supplement (DFARS) 252.235-7004 (see reference (r)) or comparable language for grants, assistance agreements, CRADAs and other agreements. Also see paragraph 4 of enclosure (4).

b. Review protocols and other submissions for compliance with Federal, DoD and DON requirements after ensuring they are properly designated as an HRPO and that they do not have a conflict of interest.

c. Confirm each non-DoD institution engaged in research involving human subjects provide required documentation, such as a Federalwide Assurance (FWA), IAIR, IIA, etc., as appropriate.

d. Identify research that may require waivers and higher-level review and approvals (e.g., 10 U.S.C. 980 waiver of informed consent, fetal research, etc.) and notify the appropriate program and contracts personnel.

e. Provide guidance regarding the potential need for additional oversight, human research protection review and approval requirements prior to award and execution of research involving human subjects. See also paragraph 4b(1) of enclosure (4) for details regarding service contracts.

f. Document the review and maintain records of determinations. Ensure records are available for site inspections and assist visits. See paragraph 15 of enclosure (4).

g. Coordinate with the Contracting or Grant Officer or ORTA and cognizant DON Program Managers to obtain submissions and information needed to perform the HRPO review.

h. Complete and document initial and continuing education and training. See paragraph 5 of enclosure (4).

i. In a timely manner, report the following to Director, DON HRPP:

(1) Notifications to a non-DoD institution by any Federal department, agency or national organization that any

part of its HRPP is under investigation for cause involving a DON-supported research protocol.

(2) UPIRTSOs in DON-supported research.

(3) All suspensions or terminations of previously approved DON-supported research protocols.

(4) The initiation and results of investigations of allegations of serious or continuing non-compliance.

j. Work with the IO to establish a formal procedure for HRPO review, including coordination with the Contracting or Grant Officer or ORTA or other staff involved in coordinating agreements to ensure that appropriate information is included in solicitations, awards, and agreements.

11. The IRB Chair and Vice Chair(s) acting in IRB Chair capacity shall be a federal employee or Service Member and shall:

a. Ensure that the IRB reviews research in accordance with the Common Rule, DoD, and DON requirements (and FDA requirements as applicable) and that it considers scientific review as required by paragraph 3b of enclosure (4).

b. Review and sign IRB meeting minutes.

c. Ensure that minutes and approval or disapproval of research protocols are appropriately documented.

d. Consult with other committees and individuals as appropriate or necessary (e.g., radiation safety, safety, biosafety, security, privacy board, legal officer).

e. Review and approve research that is eligible for expedited review, or forward to the convened IRB. The IRB Chair may delegate this authority to an experienced IRB member, who also shall be a federal employee or Service Member. Inform all IRB members of the results of expedited reviews. See paragraph 3c of enclosure (4) for details.

f. Provide prompt notification of subparagraphs (1) - (7) below to the IO whose institution is conducting the research and to the Director, DON HRPP. Upon completion of investigation,

submit reports within 15 business days (including supporting documentation, information, review, disposition, recommendations, and associated plans for corrective action) for the following:

(1) All investigations and audits of the institution's HRPP, including those conducted by outside organizations (e.g., FDA or OHRP).

(2) UPIRTSOs

(3) Events that require reporting to the FDA per reference (d): adverse events associated with use of drugs (see 21 CFR 312), adverse experiences associated with use of biologics (see 21 CFR 600), or unanticipated adverse device effects (see 21 CFR 812) or copies of reports or submissions to the FDA per reference (d).

(4) Initiation and results of investigations of serious or continuing non-compliance.

(5) Initiation and results of investigations of research misconduct.

(6) Suspensions and terminations of previously approved research protocols.

(7) Significant communications between the institution and other federal departments or agencies, State agencies, or foreign governments regarding compliance and oversight.

g. May suspend research, until the convened IRB can review the protocol, due to:

(1) UPIRTSOs

(2) Serious adverse events.

(3) Significant deviations from approved protocols.

(4) Non-compliance

(5) Other reasonable cause.

h. Have direct access to the IO as necessary.

i. Complete and document initial and continuing education and training. See paragraph 5 of enclosure (4).

j. Identify and forward to the IO research which may require higher-level approval or waivers (by Navy SG, UNSECNAV, SECNAV, ASD(R&E), or SECDEF) before the research may begin.

12. Members of DON IRBs. The primary role of the IRB member is to protect the rights and welfare of human research subjects in accordance with Federal, DoD, and DON requirements.

a. The IRB member must maintain membership status, per reference (a), enclosure (3), section 3a(7). Direct hire locally employed staff at DON overseas laboratories, as described in DoDI 1400.25 Volume 1231, are considered to be federal employees for purposes of this instruction.

b. If delegated this authority from the IRB Chair, IRB members who are federal employees or Service Members may review and approve research that is eligible for expedited review or forward to the convened IRB. See paragraph 11e of enclosure (3) and paragraph 3c of enclosure (4).

c. IRB members must complete and document initial and continuing education and training. See paragraph 5 of enclosure (4) for details.

13. The Exemption Determination Official (EDO) shall be a Federal employee or Service Member designated by the institution's IO to review proposed effort(s). The EDO shall:

a. Review protocols, test plans, proposals and other activities to determine if the proposed effort meets the definition of research involving human subjects and if so, whether research is eligible for exemption from the requirement for IRB review.

b. Document determination and, if applicable, include exemption category and rationale.

c. Submit determinations and supporting materials to IO for information and action, if appropriate, and to the Director, DON HRPP for headquarters-level administrative review.

d. Advise Principal Investigator (PI) or Program Manager of determination(s) and if the research is not eligible for exemption, recommend that the PI or Program Manager refer the effort to an IRB for further disposition.

e. Complete and document initial and continuing education and training prior to performing any HRPP related duties. See paragraph 5 of enclosure (4).

f. Maintain records of determinations. Ensure records are available for site inspections and assist visits. See paragraph 15 of enclosure (4).

14. The IRB Administrator, HRPP Support Personnel or HRPP Point of Contact (POC) may be assigned duties that vary based on the policies and practices of the institution's HRPP. The Administrator, Support Personnel or HRPP POC may be required to:

a. Coordinate IRB meetings, ensure that meeting minutes are recorded and disseminate the supporting documentation in a timely manner.

b. Advise PIs regarding protocol submission requirements.

c. Maintain records, including new protocol submissions, continuing reviews, amendments, training documents and IRB meeting minutes and records. See paragraph 15 of enclosure (4).

d. Prepare and track correspondence, assurance packages and requests for assurance renewals.

e. Coordinate site inspections, assist visits and preparation of SOPs.

f. Manage day-to-day operations of the HRPP.

g. Inform the IRB Chair of events and concerns affecting the HRPP.

h. Complete and document initial and continuing education and training. See paragraph 5 of enclosure (4).

i. The HRPP POC at DON institutions without their own IRB serves as the primary interface between investigators and reviewing officials (EDO, IRB Chair, Vice Chair, IRB, and HRPO).

j. The HRPP POC at DON institutions without their own IRB shall have direct access to the IO as necessary and meet with the IO at least annually.

15. The Principal Investigator (PI) for DON-Conducted Research shall be a current DoD civilian employee, Service Member, an individual covered under the Intergovernmental Personnel Act (IPA) or an individual appointed as an expert or consultant in accordance with 5 U.S.C. 3109 and must be assigned to or employed by a DON institution. The PI shall:

a. Supervise and assume responsibility for all research conducted under the protocol.

b. Obtain written determination of whether the proposed activity is research involving human subjects or meets criteria for exemption per reference (b) as determined by IRB Chairs, IRB Vice Chairs, EDOs or other properly designated officials in accordance with this instruction. Investigators shall not make this determination.

c. Engage only in the performance of non-exempt research involving human subjects that is covered by a DoD-DON Assurance or IIA and reviewed and approved by an IRB and IO (see paragraph 9d(8) of this enclosure). Other required institutional approvals (e.g., radiation safety, safety, biosafety, security and privacy board) shall also be obtained prior to beginning the research.

d. Obtain IRB approval prior to implementing proposed amendments to approved research.

e. Fulfill the IRB's continuing review requirements prior to the expiration date of the current IRB approval.

f. Submit final report to the IRB when research involving human subjects, including analysis of identifiable private information, is completed.

g. Coordinate with the IRB and provide all requested materials for review in a timely manner.

h. Follow IRB direction and requirements.

i. Notify the IRB in writing of possible UPIRTSOs, serious adverse events, and non-compliance; in accordance with local policies and procedures.

j. Document informed consent by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form unless a waiver of documentation or waiver of consent has been approved by the IRB and higher authority, as applicable. See paragraph 1b of this enclosure and reference (a), enclosure (3), section 9.

k. Report any potential conflicts of interest to the IRB before engaging in research involving human subjects, and when potential conflicts arise during the conduct of research.

l. Complete and document initial and continuing education and training. See paragraph 5 of enclosure (4).

m. Maintain records appropriate to the research (e.g., the study plan, consent forms, correspondence from the IRB, and data), as "project case files" per reference (m). See paragraph 15 of enclosure (4).

n. Coordinate among the engaged institutions the selection of the IRB of record and document in writing the rationale for selecting the IRB. When there will be more than one IRB review, the PI will provide justification to the IO whose assurance the work will be performed under, for the IO to forward to the Director, DON HRPP.

PROCEDURES

1. Department of the Navy (DON) Human Research Protection Program (HRPP) Management Plan. Per reference (a), enclosure (3), section 1, the DON HRPP Management Plan shall include:

a. Policies and procedures in support of reliance on a single Institutional Review Board (IRB) to review collaborative or multi-site research.

b. A requirement that institutions provide guidance to the Principal Investigator (PI) to coordinate among the engaged institutions regarding the selection of the IRB of record. The PI shall document in writing the rationale for selecting the IRB. The engaged institutions shall approve the plan for the single IRB review and shall execute Institutional Agreement(s) for IRB Review (IAIRs) as appropriate. Alternatively, when there will be more than one IRB review, the PI will provide justification to the Institutional Official (IO) with the assurance covering the research for the IO to forward to the Director, DON HRPP.

c. A requirement for identification and management of personal and financial conflicts of interest by DON personnel. As Executive Agency employees and military, DON researchers and HRPP personnel must also follow applicable Federal regulations and the Joint Ethics Regulation DoD 5500.07-R.

2. Requirements for a Department of Defense (DoD)-DON Assurance. Per reference (a), enclosure (3), section 2:

a. For purposes of DON-conducted research and processing of a DoD-DON Assurance, an institution should be defined at the highest level possible to assure appropriate oversight of the research.

(1) However, the institution shall ensure that key individuals within the HRPP (e.g., the IRB Chair) have access to the IO. The IO must be aware of the research activities of the institution.

(2) An institution should carefully consider extending its assurance to include individuals from institutions that are outside the authority of the IO. If it decides to do so, then documentation (e.g., an Individual Investigator Agreement (IIA)) shall be executed.

Enclosure (4)

(3) DoD-DON Assurance packages, including education and training documentation, shall be submitted to the Director, DON HRPP for processing and forwarded to the Navy Surgeon General (Navy SG) for approval.

(4) Renewal packages for DoD-DON Assurances shall be submitted to the Director, DON HRPP no later than 60 calendar days prior to expiration of the assurance.

(5) Renewal packages due to change in IO shall be submitted to Director, DON HRPP within 30 calendar days after the new IO assumes duties.

(6) Updated documentation, including Human Research Protection Official (HRPO) and Exemption Determination Official (EDO) appointment letters, significant changes to the institution's policies or changes to the IRB Chair, shall be submitted to Director, DON HRPP.

b. For purposes of DON-supported research conducted by non-DoD institutions:

(1) Institutions seeking DON support for non-exempt research involving human subjects shall submit and maintain a Federal assurance acceptable to the DON.

(2) The HRPO shall determine if the existing Federal assurance is appropriate for the specific research protocol.

c. DON institutions that do not meet criteria for requiring a DoD-DON Assurance, but must establish an HRPP because they conduct exempt research or support research, may rely on ad-hoc support (e.g., HRPO, EDO) provided by the Director, DON HRPP or designated officials in another DON institution. This arrangement shall be documented in an agreement executed by the IO(s) with the endorsement of the Director, DON HRPP. This agreement becomes the basis for the institution's HRPP. The IO shall ensure that information about the agreement is communicated to the appropriate personnel.

3. DON-Conducted Research Involving Human Subjects: In addition to reference (a), enclosure (3), section 3, an institution's policies and procedures shall include the designation, oversight and appropriate training of DON personnel.

a. DON institutions shall develop policies and procedures regarding the identification, training and designation of EDOs. These policies and procedures shall be submitted to the Director, DON HRPP for acceptance. Various Federal employees or Service Members can be identified as the EDO, such as HRPOs, IRB members, IRB Administrators or other designated officials. See enclosure (5) for definition of EDO.

(1) Proposed changes to a protocol already determined to be exempt shall be resubmitted for EDO review prior to implementation.

(2) The DON institution shall retain all records as "project case files," per reference (m).

b. Scientific review of non-exempt research involving human subjects is an independent review that must be conducted prior to IRB review. DON institutions must develop policies and procedures describing evaluation of proposed research for scientific or scholarly validity. Scientific review can be conducted in a variety of ways appropriate to the research and the Command. The review can be conducted by a group such as a committee or board, or by single knowledgeable individual(s). At a minimum, scientific review must meet applicable conflict of interest rules and regulations, and should consider the significance of the research, the adequacy of the approach used in the research and the competence of the investigator to conduct such research. The institution's policies and procedures must ensure consideration of scientific review during the IRB review process per reference (a), enclosure (3), section 3a(2) and paragraph 9d of enclosure (3) of this instruction.

c. IRBs may use expedited review procedures under section 219.110 of reference (b) for certain kinds of research involving no more than minimal risk and for minor changes in approved research. See Volume 63, Number 216, pages 60364-60367, Federal Register, November 9, 1998 and reference (a), enclosure (3), section 3a(3)

(1) When appropriate, the IRB Chair shall conduct or delegate to an experienced IRB member who is a Federal employee or Service Member the authority to conduct expedited

review and approve research protocols that meet the criteria at section 219.110 of reference (b). This authority may not be further delegated.

(2) The results of the expedited review shall be reported to the IRB. The information reported to the IRB will include, at minimum:

(a) The title of the protocol.

(b) The name and organizational affiliation of the PI.

(c) If applicable, the name and organizational affiliation of the Research Monitor. See reference (a), enclosure (3), section 8.

(d) The expedited category under which the protocol was approved.

(e) The period of approval and the protocol expiration date.

(f) An abstract of the protocol.

(g) Brief summary of the set of minor changes approved under 32 CFR 219.110(b)(2) to allow for confirmation regarding eligibility as minor changes.

(h) Information regarding waivers of informed consent or waiver of documentation of informed consent, and any unusual or special circumstances presented by the research, as applicable.

d. When the research involving human subjects is being conducted in a foreign country whose laws and regulations are applicable to that research, the DON institution shall confirm that all applicable national laws and requirements of the foreign country have been met in addition to the requirements in this instruction. The IRB shall also consider the cultural sensitivities in the setting where the research will take place.

(1) When this paragraph is applicable, these requirements must be met before the IRB approves research involving humans per the requirements of sections 219.103, 219.107, and 219.111 of reference (b).

(2) Strategies for the institution to confirm that the research is compliant with all applicable laws and requirements of the foreign country may include, but are not limited to:

(a) Consulting with a local human research protection expert (e.g., ethics review board) within the country where the research will take place.

(b) Consulting with the country's health ministry, consulate, embassy or other government official with knowledge of the nation's human research protection requirements (e.g., a local Ministry of Health or other point of contact provided via the Office of Human Research Protections' International Compilation of Human Research Standards).

(c) Establishing collaborative relationships with a foreign university or institution.

(d) Coordinating with Navy's International Program Office, Marine Corps Systems Command International Programs, or Judge Advocate General (JAG) Code 10 to determine if an existing international agreement applies, and complying with the requirements of SECNAVINST 5710.25B prior to initiating or conducting negotiations for an international agreement.

(e) Consulting with reputable and knowledgeable Non-Governmental Organizations (NGOs) or Community-Based Organizations (CBOs).

(f) Consulting with researchers independent of the research team who are experienced in conducting research involving human subjects in the country where the work will take place.

(3) The IRB, in their consideration of the cultural sensitivities of the subject population, may use information from all individuals and organizations. See paragraph 3(d)2 of this enclosure. The IRB can also use written materials and/or discussions with appropriate consultants who may participate in convened IRB meetings, but may not vote.

e. For other relevant reviews (e.g., radiation safety, safety, biosafety, and privacy board), the DON institution shall have policies and procedures to ensure the research involving human subjects has been approved by all required organizations

before human subjects are recruited or any other research activities with human subjects begin. The IRB may approve a research protocol contingent upon its approval by other organizations. To the extent possible, safety reviews and other reviews that the IRB should consider in order to fulfill its responsibilities should be obtained prior to IRB review. However, reviews can be conducted in parallel. Attitude and opinion surveys must be approved when required by the Office of Management and Budget DoD, Navy and Marine Corps survey officials prior to being conducted. After those approvals have been obtained, the IRB should be provided with documentation of those approvals.

(1) When a DON IRB reviews research to take place at other institutions or with subject populations unfamiliar to the IRB, it may be necessary for the IRB to direct the PI to obtain information so the IRB can understand any local concerns.

(2) When a DON IRB reviews research that recruits subjects from other DoD institutions, the IRB may direct the PI to obtain information from the institution in support of the IRB's understanding of local context and to confirm that the institution's chain of command agrees to allow the research to be conducted at their institution.

f. The DON IRB shall confirm that each institution engaged in the conduct of non-exempt research involving human subjects is working under an appropriate assurance.

(1) When an investigator has multiple DoD or DON institutional affiliations (e.g., an employee of a medical center is also an adjunct faculty at a DoD Service academy), the PI shall identify which of these institutions is engaged in the conduct of research per reference (b).

(2) In cases where the research is conducted in the investigator's official capacity under a DoD Assurance, other institutions to which the investigator may also be affiliated, but which are not supporting the research, are not engaged in the research; therefore are not responsible for oversight of the research.

g. For purposes of DON IRB membership, contractors (other than consultants or experts appointed under 5 U.S.C. 3109), retired federal employees, retired employees of any other state,

or local government agency and retired Service members do not meet DON IRB membership requirements.

h. DON institutions seeking to rely upon a non-DoD institution's IRB should work with the Director, DON HRPP in advance of the submission of the DON Component administrative review (identified per reference (a), enclosure (3), section 3b) package to ensure the arrangement is appropriate.

i. When a DON Component-level administrative review (see paragraph 1a of enclosure (5)) must be conducted before the research involving human subjects can begin (identified per reference (a), enclosure (3), section 3b), the DON institution must submit to the Director, DON HRPP the following documentation:

(1) An explanation of why the institution is submitting the study for review citing one of the paragraphs per reference (a), enclosure (3), section 3b (e.g., requesting DON Component-level administrative review of fetal research per reference (a), enclosure (3), section 3b(1)(d)).

(2) Documentation regarding appropriate Federal assurance coverage (i.e., DoD Assurance, Federalwide Assurance (FWA), IIA).

(3) The IRB approval letter, including protocol and informed consent document.

(4) Any documentation of justification for IRB approval of waiver of consent, waiver of consent elements, or waiver of written consent per reference (b), 219.116 or 117.

(5) Other IRB approved documents and other supporting documents considered by the IRB.

(6) If conducted in a foreign country, all documentation confirming compliance with applicable laws and regulations of the foreign country.

4. Research Involving Human Subjects Conducted by a Non-DoD Institution. Per reference (a), enclosure (3), section 4:

a. Non-DoD institutions engaged in non-exempt research involving human subjects shall provide required documentation, such as their FWA.

b. The non-DoD institution shall comply with the terms of the Defense Federal Acquisition Regulation Supplement (DFARS) clause in the contract or comparable language used in the grant, assistance agreement, CRADA or other agreements with the DON institution supporting the research involving human subjects, as provided per reference (a), enclosure (3), section 4a(1).

(1) The non-DoD institution shall submit this documentation prior to award of the research involving human subjects for contracts, grants, CRADAs and other agreements. Service contracts (as defined by the Federal Acquisition Regulation section 37.101) that are for dedicated on-site support Services personnel or other circumstances where it is necessary to separate tasks involving human subjects from other work which does not, must formally separate such tasks into separate options that cannot be exercised until all documentation is provided and approved by the cognizant HRPO.

(2) The non-DoD institution must submit to program office personnel and to the HRPO (via contracting officer, grants officer, or Office of Research, Technology and Applications (ORTA), as applicable), documentation of special determinations such as waivers made by the IRB when the IRB approves protocols recruiting populations identified in reference (a), enclosure (3), section 7, "Additional Protections for Human Subjects," (e.g., pregnant women, prisoners, children, DoD personnel).

(3) When asserting an activity is not research involving human subjects or is exempt, the non-DoD institution shall submit to the HRPO via the Contracting Officer (or Grant Officer or ORTA as applicable) and program office personnel, the non-DoD institution's determination letter and any supporting documentation considered by the institution in making the determination. The determination letter shall provide a justification for the determination made supported by relevant facts and regulatory citations (e.g., applicable exempt category per reference (b), section 219.101(b)).

(4) If not included in the protocol, an IRB approved informed consent document must also be submitted, except when not required consistent with law and regulation.

c. The non-DoD institution shall comply with reference (a), enclosure (3), section 4b(4) by submitting required documentation for the HRPO's review and consideration, including significant and substantive changes as defined in enclosure (5). The HRPO shall file documents submitted and take any appropriate action.

d. In addition reference (a), enclosure (3), section 4c:

(1) The HRPO must be a federal employee or Service member sufficiently qualified through experience, expertise and training to be able to review contractor documentation.

(2) The HRPO shall communicate directly with the DON institution supporting the research regarding all activities reviewed under this section. The DON institution supporting the research shall notify the non-DoD institution regarding any action required consistent with applicable requirements (e.g., contracts, grants, CRADAs, other agreements).

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

(a) Strategies that a non-DoD institution may use to confirm that all applicable national laws and requirements of the foreign country have been met may include, but are not limited to, establishing collaborative relationships with a foreign university or institution, consulting with the country's health ministry, consulate, or embassy, working with NGOs or CBOs in the area where the research will be conducted, or with researchers independent of the research team who are experienced in conducting research involving human subjects in the country where the work will take place. Additionally, information about laws and guidelines in a number of countries can be found in the Office of Human Research Protections (OHRP) International Compilation of Human Research Standards.

(b) Non-DoD institutions shall document compliance with this requirement and provide supporting materials to the HRPO.

(c) The IRB shall seek information on any issues specific to the targeted population (e.g., cultural

sensitivities, religious issues, language) that may add risk to the research.

5. Education and Training Requirements. Per reference (a), enclosure (3), section 5, training requirements are identified in reference (s). Additional guidance may be promulgated separately by the Director, DON HRPP.

6. Selection of Human Subjects and Evaluating Risk. Per reference (a), enclosure 3, section 6, all waiver requests shall be forwarded to Director, DON HRPP for processing. Submissions required in this section shall not be made directly to ASD(R&E).

7. Additional Protections for Human Subjects. Per reference (a), enclosure (3), section 7:

a. All waiver requests and requests for approval shall be forwarded to Director, DON HRPP for processing. Submissions required in this section shall not be made directly to ASD(R&E). See reference (a), enclosure (3), section 7.

b. When DON personnel are the targeted subject population, the IRB shall review and approve the recruitment process to ensure compliance with DoD and DON requirements. A DON IRB review of research being conducted by a non-DoD institution is not required solely because DON personnel are the targeted subject population. Other additional reviews are discouraged.

c. When the research is supported by the DON and the targeted subject population consists of DoD personnel, written DoD institutional permission is required before the research can begin.

d. Activities per reference (a), enclosure (3), section 7c(2) shall be forwarded to the Navy SG for approval. Forward packages to Director, DON HRPP for processing.

8. Research Monitor. Per reference (a), enclosure (3), section 8.

9. Unique DOD Limitations on Waiver of Informed Consent. Per reference (a), enclosure (3), section 9:

a. 10 U.S.C. 980 applies not only when DoD appropriated funds are directly used to fund the research but also when DoD

personnel are involved in support of the research (e.g., researchers, subjects) and when DoD equipment, facilities, data, etc. are used (see enclosure (5) for definition of DON-supported research involving human subjects).

b. Requests for waiver shall not be made directly to ASD (R&E), but should be coordinated through the DON institution supporting the research and the Director, DON HRPP. The Navy SG will review and, if appropriate, forward requests for waiver to the Secretary of the Navy (SECNAV).

10. Protecting Human Subjects from Medical Expenses if Injured. In addition to reference (a), enclosure (3), section 10:

a. Requests for waiver per reference (a), enclosure (3) section 10c(3) shall be approved by the IO. See also paragraph 9(d)13 of enclosure (3).

b. Institutions proposing to use Secretarial Designee Program as described by section 108.4(i) of reference (t) and 32 CFR 728.77, reference (u) shall coordinate with Director, DON HRPP.

11. Compensation to Human Subjects for Participation in Research. Per reference (a), enclosure (3), section 11.

12. Service Members and Their Status as Adults. Per reference (a), enclosure (3), section 12.

13. Classified Research Involving Human Subjects. In addition to reference (a), enclosure (3), section 13, forward packages to Director, DON HRPP for processing.

14. Additional Protections for Confidentiality. In addition to reference (a), enclosure (3), section 14, proposals for using the authority under the Confidential Information Protection and Statistical Efficiency Act (CIPSEA) or a Certificate of Confidentiality shall be coordinated in advance with the Director, DON HRPP.

15. Records Management. In addition to reference (a), enclosure (3), section 15 (Record Keeping), DON institutions shall retain records in accordance with "project case file" requirements in reference (m).

16. Non-compliance With This Instruction. In addition to reference (a), enclosure (3), section 16:

a. All findings of serious or continuing non-compliance with this instruction that have been substantiated by inquiry or investigation by the Director, DON HRPP, based on findings provided by the institution, shall be reported to the ASD(R&E) in a timely manner. Submissions shall not be made directly to ASD(R&E) but should be coordinated through the DON institution's chain of command to the Director, DON HRPP.

b. The Navy SG will submit the required reports to ASD(R&E) with copy to ASN(RD&A), along with recommendations.

17. Applicability to Other Requirements. Per reference (a), enclosure (3), section 17, research shall not begin until there is IRB approval, all other approvals are in place (e.g., surveys, radiation safety), and institutional approval has been obtained. Additionally, research involving human subjects may be subject to other Federal, DoD, or DON requirements such as DoDI 1000.30, "Reduction of Social Security Number Use Within DoD," DoD 6025.18-R, "DoD Health Information Privacy Regulation," DoD 5400.11-R, "Department of Defense Privacy Program," SECNAVINST 5211.5E, "DON Privacy Program."

18. Coordinating Committee for Human Research Protection Programs (CCHRPP) Membership. See reference (a), enclosure (3), section 18.

DEFINITIONS

These terms and their definitions are for the purpose of this instruction.

1. Administrative Review. A review of a research protocol and supporting documents (e.g., safety review, scientific review, IRB minutes) related to DoD-supported research involving human subjects which ensures the institution engaged in the research involving human subjects has met the requirements of all applicable regulations and policies. This review is NOT an IRB review.

a. Department of the Navy (DON) Component-Level Administrative Review. The DON Component-level administrative review that must be conducted before non-exempt research involving human subjects can begin per reference (a), enclosure (3), section 3b.

b. Headquarters-Level Administrative Review. Administrative review of approved research protocols to verify regulatory compliance with Federal, DoD and DON research protection requirements. This review does not have to be complete before the research begins.

c. Human Research Protection Official (HRPO) Administrative Review. This review is conducted by the HRPO per reference (a), enclosure (3), sections 4c(1) and (2) before research involving human subjects can begin.

2. Adverse Event. An adverse event is any untoward or unfavorable occurrence associated with the conduct of a research project, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. For Food and Drug Administration (FDA)-regulated research, the definition of adverse event should be followed. See reference (d).

3. Assurance. See "federal assurance."

4. Classified Research Involving Human Subjects. Research involving human subjects where the protocol or other information

required by the IRB for review and oversight or required or provided by the research subjects includes classified information, as defined in reference (v).

5. Clinical Investigations. Any research or experiments that involve a test article, one or more human subjects, and are performed under the requirements of section 50 of reference (d). Clinical investigations are a subcategory of research involving human subjects.

6. Clinical Research Involving Human Subjects. For the purpose of reference (a), enclosure (3), section 6a, "Selection of Human Subjects," the term, "clinical research involving human subjects," is synonymous with the term "clinical investigations" defined above.

7. Common Rule. The regulation adopted by multiple Federal departments and agencies for the protection of human subjects in research. The DoD's implementation of the Common Rule is 32 Code of Federal Regulations (CFR) part 219; the Department of Health and Human Services' implementation of the Common Rule is subpart A of 45 CFR part 46.

8. Continuing Non-compliance. A pattern of non-compliance (see non-compliance) that suggests the likelihood that, without intervention, instances of non-compliance will recur. A repeated unwillingness to comply with this instruction or a persistent lack of knowledge of how to comply with this instruction.

9. Detainee. Defined in DoD Directive 2310.01E, "The Department of Defense Detainee Program," August 19, 2014 as "Any individual captured by, or transferred to the custody or control of, DoD personnel pursuant to the law of war". This does not include persons being held solely for law enforcement purposes, except where the United States is the occupying power. Detainees who are U.S. citizens or U.S. resident aliens will continue to enjoy all applicable rights and privileges under U.S. law and DoD regulations."

10. DoD Personnel. DoD civilian employees and members of the Military Services. DON personnel is a subset of DoD personnel.

a. DoD Civilian Employee. An individual meeting the definition of "employee" consistent with section 2105 of Title

5, U.S.C. It includes employees of DoD Non-Appropriated Fund Instrumentalities; DoD civilian employees filling full-time, part-time, intermittent, or on-call positions; and individuals serving under personal services contracts consistent with section 2.101 of Title 48, U.S.C. It excludes employees of contractors (other than personal services contractors) and foreign nationals of host countries.

b. Service Members. Individuals appointed, enlisted or inducted for military service under the authority of the DoD. The Military Services are the Army, the Navy, the Air Force, the Marine Corps, the Coast Guard and the Reserve Components, which includes the Army and the Air National Guards of the United States. Members of the Reserve Components are included when in a duty status.

11. DON-Conducted Research Involving Human Subjects. Research involving human subjects that is performed by DON personnel. DON-conducted research is one type of DON-supported research involving human subjects. See "engaged in research involving human subjects."

12. DON-Supported Research Involving Human Subjects. Research involving human subjects for which the DON is providing at least some of the resources (see "research involving human subjects"). 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 DON personnel for recruitment or identifiable data or specimens from living individuals. It includes both DON-conducted research involving human subjects and research involving human subjects conducted by a non-DON institution.

a. An activity is not considered to be DON-supported when DON personnel have been formally granted authorization to pursue an outside activity that is separate from their DON position and which does not otherwise involve the DON. An activity is also not considered to be DON-supported when DON personnel are in an off-duty status or otherwise not working in a DON capacity or conducting research under a DoD-DON Assurance.

b. Additionally, legal transfer through sale or donation of a piece of equipment from the DON to an outside organization, which would sever the relationship to the DON, would not be

considered to be DON-supported if the transfer is not for the purpose of enabling a specific human subject research protocol.

13. Engaged in Research Involving Human Subjects. An institution is engaged in research involving human subjects when its personnel are conducting activities covered by section 219.101(a) of reference (b) and this instruction. An institution that is 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 is not engaged in the research involving human subjects (but is supporting the research (see "DON-supported research involving human subjects"))).

14. Exempt Research Involving Human Subjects. Research involving human subjects where the only involvement of the human subjects in the research will be in one or more of the categories identified in section 219.101(b) of reference (b).

15. Exemption Determination Official (EDO). Serves as a local Human Research Protection Program (HRPP) official designated by the Institutional Official (IO) for the purposes of reviewing the institution's proposed activities with humans and making official determinations regarding whether an activity (1) is research involving human subjects, (2) meets exemption criteria per reference (b), section 219.101(b) or (3) is research involving human subjects that requires IRB review. EDOs must be Federal employees or Service members who are sufficiently qualified through training or experience to be able to ascertain the acceptability of a proposed activity, while being sufficiently removed from the activity to avoid the appearance of a conflict of interest.

16. Experimental Subject. See "research involving a human being as an experimental subject."

17. Federal Assurance. A written document in which an institution (not an IRB) commits to a Federal department or agency their compliance with the requirements set forth in the Common Rule. Institutions engaged in non-exempt research involving human subjects conducted or supported by the DoD or other Federal departments and agencies that have adopted the Common Rule must have a Federal assurance approved or accepted

by the Federal agency supporting the research. The elements of a Federal assurance are outlined in section 219.103(b) of reference (b).

18. Federal Employee. An individual meeting the definition of "employee" consistent with section 2105 of Title 5, U.S.C.

19. Human Research Protection Official (HRPO). An individual who has the responsibilities as defined in paragraph (a)(2) of section 252.235-7004 of reference (r). The HRPO must be a Federal employee or Service member designated by the DON institution. There may be more than one HRPO in a DoD Component. Some DoD Components may use a different title for the person(s) with the defined responsibilities.

20. Human Research Protection Program (HRPP). An institution's system of interdependent elements that implement policies and practices to protect human subjects involved in research. A HRPP may or may not include a Federal assurance. If the HRPP includes a Federal assurance, it may contain policies and procedures for an IRB belonging to the institution or for a relationship with an IRB external to the institution.

21. Human Subject. A living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or obtains identifiable private information as defined in section 219.102(f) of reference (b). (FDA regulations include a different definition of human subject. With respect to research subject to FDA regulations, the FDA definition in section 50.3(g) of reference (d) also applies.)

22. Identifiable Private Information. Defined in section 219.102(f) of reference (b).

23. Individual Investigator Agreement (IIA). A DoD-harmonized agreement which allows an individual from a Command/institution not holding an assurance to conduct research involving human subjects under the assurance of a Command/institution who is engaged. Agreements can cover one, several or all protocols with which the investigator is involved.

24. Institution. An organization or entity defined in a Federal assurance or HRPP.

25. Institutional Agreement for IRB Review (IAIR). A DoD-harmonized agreement which allows a Command/institution engaged in research involving human subjects to rely upon the IRB services of another Command/institution. An IAIR can cover one, several or all protocols in which the Command/institution is engaged.

26. Institutional Official (IO). The senior person authorized to establish and responsible to maintain the HRPP for the DON institution. The IO is a senior military or civilian official with the authority to commit the institution to comply with Federal, DoD and Component requirements. The IO is responsible for its institutions' Federal assurance and the IRBs internal to the institution, if these elements are part of the HRPP. The IO heads the DON institution's HRPP. The IO, often a Flag-, General or Senior Executive Service (SES)-level official, frequently serves as the Commander, Commanding Officer, Officer in Charge or Senior Official at an institution.

27. Intervention and Interaction. An intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. See section 219.102(f) of reference (b) for more information. Examples include, but are not limited to, a physical procedure, a drug, a manipulation of the human subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose, or communication such as a survey or interview.

28. Intramural Research. Research (see "research involving human subjects") that is conducted by an entity that is part of the DoD.

29. Non-compliance. Failure of a person, group or institution to act in accordance with this instruction, its references or applicable requirements.

30. Non-DoD Institution. An entity that is not part of the DoD.

31. Non-Exempt Research Involving Human Subjects. An activity that meets the definitions of research and human subject, but does not meet the criteria where the only involvement of the

human subjects in the research are in one or more of the categories identified in section 219.101(b) of reference (b).

32. Operational Test & Evaluation (OT&E). Defined in section 139(a)(2)(A) of reference Title 10, U.S.C.

33. Principal Investigator (PI). The person responsible for the execution of the research protocol and the performance of the research team.

34. Prisoner. Defined in Part 46, subpart C of Title 45, Code of Federal Regulations. Includes military personnel in either civilian or military custody or detainment.

35. Private Information. Defined in section 219.102(f) of reference (b).

36. Research. Any activity that is a systematic investigation, including Research, Development, Testing, and Evaluation (RDT&E), designed to develop or contribute to generalizable knowledge as defined in section 219.102(d) of reference (b).

37. Research Involving Human Subjects. Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by section 219.101(a) of reference (b) (including exempt research involving human subjects) and this instruction. The following activities conducted or supported by the DoD are NOT research involving human subjects:

a. Activities 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 DoD, including health surveillance per reference (e) and the use of medical products per reference (f).

b. Authorized health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment.

c. Activities performed for the sole purpose of medical quality assurance consistent with section 1102 of Title 10, U.S.C. and reference (h).

d. Activities performed solely for an OT&E project where the activities and project meet the definition of OT&E as defined in section 139(a)(2)(A) of Title 10, U.S.C.

e. Activities 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. Activities, 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. Survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by reference (j).

38. Research Involving a Human Being as an Experimental Subject. 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. This definition relates only to the application of section 980 of Title 10, U.S.C. it does not affect the application of section 219 of reference (b). This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of reference (b), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

39. Research Misconduct. Defined in DoD Instruction 3210.07, "Fabrication, falsification, or plagiarism in proposing,

performing, or reviewing research, or in reporting research results. Research misconduct does not include honest error or differences of opinion."

40. Research Monitor. An individual with expertise consonant with the nature of risk(s) identified within the research protocol, whose role is to protect the safety and well-being of human subjects. This individual shall be independent of the team conducting the research involving human subjects. See reference (a), enclosure 3, section 8.

41. Secretarial Designee Program. Defined in references (t) and (u).

42. Serious Adverse Event. For FDA-regulated research, the definition of serious adverse event should be followed. See reference (d).

43. Serious Noncompliance. Failure of a person, group, or institution to act in accordance with this instruction and its references such that the failure could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of research data.

44. Significant Change. An amendment to research conducted by a non-DoD institution that requires prompt notification to the HRPO per reference (a), enclosure (3), section 4b(4). This includes all substantive changes (see "substantive change"), including change in PI, major non-administrative amendments (e.g., changes in protocol design) and administrative changes that affect the HRPO's ability to adequately oversee the research.

45. Substantive Change. An amendment to research conducted by a non-DoD institution that requires HRPO review and acceptance after IRB review to ensure continuing compliance with applicable DoD and DON requirements per reference (a), enclosure (3), section 4c(2)(c). Substantive changes are a subset of significant changes. This includes but is not limited to:

a. Addition of any condition identified per reference (a), enclosure (3), section 3b(1).

b. Addition of any condition that may impact issues initially reviewed by the HRPO per reference (a), enclosure (3), section 4c(2), including:

(1) Addition of personnel representing institutions not identified upon initial HRPO review.

(2) Change in the IRB's review procedure (e.g., from exempt to expedited, expedited to convened board, etc.).

(3) Change in research related activities that significantly affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study.

(4) Addition of subjects who cannot provide informed consent (see references (b), (k) and (l)).

(5) Addition of a research site in a foreign country and will include non-DoD personnel or non-U.S. citizens as human subjects.

46. Test Article. Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

47. Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO). 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 (in this instruction, 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).

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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.

REPORTS CONTROL

1. The reporting requirements contained in this instruction are exempt from reports control per Part IV of SECNAV M-5214.1 of December 2005. The specific exemptions are applied as follows:

a. Enclosure (3), paragraph 2b(4) is sponsored by the Department of Health and Human Services and is assigned Office of Management and Budget (OMB) Reports Control Number 0990-0260.

b. Enclosure (3), paragraphs 2a(1) and 4o are exempt from information control per SECNAV M-5214.1 PART IV, Paragraph 7g.

c. Enclosure (3), paragraph 3b and 3c; paragraph 4k; paragraphs 8l through 8n; paragraphs 9d(4)(b); paragraph 9d(10)(a) through (e); paragraph 10a, paragraph 10i(4); paragraph 11f(3); and paragraph 15i exempt from information control per SECNAV M-5214.1 PART IV, Paragraph 7n.

d. Enclosure (3), paragraph 5a is exempt per SECNAV M-5214.1 PART IV, Paragraph 7j.

e. Enclosure (3), paragraphs 5b, paragraph 9d(10)(f) and 9d(10)(g) and paragraphs 9d(11), 9e(1), 9f(4), 11f(1), 15f and 3c(2) is exempt per SECNAV M-5214.1 PART IV, Paragraph 7k.

f. Enclosure (3), paragraphs 9c(1)(b)4 and enclosure (4), paragraph 3e are exempt from information control per SECNAV M-5214.1 PART IV, Paragraph 7l.

2. Enclosure (3), paragraphs 3a through 3e; paragraphs 4g through 4k, 4l through 4n and paragraph 8k; and enclosure (4) paragraph 16b is assigned SECNAV Report Control Symbol 3900-2.