



Defense Health Agency

ADMINISTRATIVE INSTRUCTION

NUMBER 3216.01

May 31, 2023

Incorporating Change 1, January 3, 2025

DAD-R&E

SUBJECT: Protecting Human Subjects in Research

References: See Enclosure 1.

1. PURPOSE. This Defense Health Agency-Administrative Instruction (DHA-AI), based on the authority of References (a) and (b), and in accordance with the guidance of References (c) through (an), establishes the Defense Health Agency's (DHA) oversight procedures for all DHA conducted or supported research with humans, human data, or human specimens.

2. APPLICABILITY. This DHA-AI, in accordance with Section 1073c of Reference (d), applies to: Military Medical Treatment Facilities (MTF), DHA Human Research Protection Programs (HRPP), DHA Institutional Review Boards (IRB), and all other organizational entities within the purview of the DHA Office of Research Protections' (ORP) research enterprise. All personnel to include: assigned or attached active duty and Reserve Component Members, members of the Commissioned Corps of the Public Health Service, federal civilians, contractors (when required by the terms of the applicable contract), and other personnel assigned temporary or permanent duties at DHA and DHA Activities (under the authority, direction, and control of DHA).

3. POLICY IMPLEMENTATION. It is DHA's instruction, pursuant to References (c) through (an), to:

a. Provide for the protection of volunteer human subjects in research conducted, supported, or assisted by the DHA.

b. Implement standardized procedures for comprehensive oversight of all research involving human subjects, activities that constitute research and those that are excluded because they are not research per References (e) and (f).

c. Implement reporting requirements and standards for institutions that are subject to the provisions of this DHA-AI.

4. RESPONSIBILITIES. See Enclosure 2.

5. PROCEDURES. See Enclosure 3.

6. PROPONENT AND WAIVERS. The proponent of this publication is the Deputy Assistant Director (DAD), Research and Engineering (R&E). When Activities are unable to comply with this publication the activity may request a waiver that must include a justification, to include an analysis of the risk associated with not granting the waiver. The Activity Director or senior leader will submit the waiver request through their supervisory chain to the DAD-R&E to determine if the waiver may be granted by the Director, DHA or their designee.

7. RELEASABILITY. **Cleared for public release.** This DHA-AI is available on the Internet from the Health.mil site at: <https://health.mil/Reference-Center/Policies> and is also available to authorized users from the DHA SharePoint site at: <https://info.health.mil/cos/admin/pubs/SitePages/Home.aspx>.

8. EFFECTIVE DATE. This DHA-AI:

a. Is effective upon signature.

b. Will expire 10 years from the date of signature if it has not been reissued or cancelled before this date in accordance with Reference (c).

9. TEMPLATES. Templates referenced in this document can be retrieved from: <https://www.milsuite.mil/book/groups/office-of-research-protections-orp-dha> or <https://www.health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Engineering/Research-Protections>

a. DoD Assurance Request Template

b. DoD Template Individual Investigator Agreement (IIA) Template

10. SUMMARY OF CHANGES. Removed Appendix 2, the Assurance Cycle Flow Chart. Addressed all administrative changes required by Department of Defense Office for Human Research Protections including word choices.

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ENCLOSURE 1

REFERENCES

- (a) DoD Directive 5136.01, "Assistant Secretary of Defense for Health Affairs (ASD(HA))," September 30, 2013, as amended
- (b) DoD Directive 5136.13, "Defense Health Agency (DHA)," September 30, 2013, as amended
- (c) DHA-Procedural Instruction 5025.01, "Publication System," April 1, 2022
- (d) United States Code, Title 10
- (e) DoD Instruction 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -Supported Research," April 15, 2020
- (f) Code of Federal Regulations, Title 32
- (g) United States Code, Title 42
- (h) Code of Federal Regulations, Title 45
- (i) Public Law 107-347, "E-Government Act of 2002," December 17, 2002
- (j) Federal Register, Volume 72, Issue 115, June 15, 2007
- (k) OASD (R&E) Memorandum entitled, "Minimum Education Requirements for DoD Personnel Involved in Human Research Protection," (MERF), August 16, 2012
- (l) DoD Instruction 6000.08, "Defense Health Program Research and Clinical Investigation Programs," January 22, 2014, as amended
- (m) "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research," April 18, 1979
- (n) Code of Federal Regulations, Title 21
- (o) DoD Instruction 8910.01, "Information Collection and Reporting," May 19, 2014, as amended
- (p) DoD Manual 8910.01, Volume 1, "DoD Information Collections Manual: Procedures for DoD Internal Information Collections," June 30, 2014, as amended
- (q) DoD Manual 8910.01, Volume 2, "DoD Information Collections Manual: Procedures for DoD Public Information Collections," June 30, 2014, as amended
- (r) DoD Instruction 1100.13, "DoD Surveys," January 15, 2015, as amended
- (s) Federal Register, Volume 68, No. 119, Pages 36929-36931, June 20, 2003
- (t) DoD Directive 2310.01E, "DoD Detainee Program," March 15, 2022
- (u) United States Code, Title 5, Parts 5101 to 5949, October 28, 2004
- (v) United States Code, Title 24, Part 30, July 30, 1941
- (w) OASD Memorandum, "DoD Acceptance of Department of Health and Human Services (DHHS) Issued Certificates of Confidentiality (CoC)," August 17, 2015
- (x) DoD Manual 6025.18, "Implementation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in DoD Health Care Programs," March 13, 2019
- (y) Code of Federal Regulations, Title 48
- (z) United States Code, Title 44
- (aa) Code of Federal Regulations, Title 36

- (ab) DoD Instruction 5015.02, “DoD Records Management Program,” February 24, 2015, as amended
- (ac) Office of the Chief Management Officer-Administrative Instruction 15, “OSD Records and Information Management Program,” May 3, 2013, as amended
- (ad) DoD Manual 6055.18, “Safety Standards for Microbiological and Biomedical Laboratories,” August 11, 2020
- (ae) The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), April 2019
- (af) DoD Instruction 6025.23, “Health Care Eligibility Under the Secretarial Designee (SECDES) Program and Related Special Authorities,” September 16, 2011, as amended
- (ag) OUSD(R&E) Memorandum, “DoD Acceptance of Department of Health and Human Services (DHHS) Issued Certificates of Confidentiality (CoC),” August 27, 2015
- (ah) USD(P&R) Memorandum, “Repeal of Don’t Ask Don’t Tell and Future Impact on Policy,” January 28, 2011
- (ai) U.S. Department of Health and Human Services Food and Drug Administration Procedural Guidance “E6(R2) Good Clinical Practice: Integrated Addendum to International Conference on Harmonization E6(R1) Guidance for Industry,” March 2018
- (aj) Office of Human Research Protections Guidance, “Unanticipated Problems Involving Risks & Adverse Events Guidance,” January 15, 2007
- (ak) DHA-Technical Manual 3200.02, “Scientific Review of Clinical Investigations in Military Medical Treatment Facilities,” June 7, 2021
- (al) DHA DAD(R&D) Memorandum, “Mandatory Use of the Electronic Institutional Review Board,” April 7, 2021
- (am) Public Law 114-255, “21st Century Cures Act,” December 13, 2016
- (an) DHA-Administrative Instruction 3200.01, “Research Subject Compensation,” April 28, 2022

ENCLOSURE 2

RESPONSIBILITIES

1. DIRECTOR, DHA (COMPONENT HEAD). The DHA Director is a Component Head, who will ensure compliance with Reference (e).

2. SENIOR DESIGNATED OFFICIAL (SDO). The DHA DAD-R&E is the SDO, who will:
 - a. Assume the responsibilities for the management of the Component Office of Human Research Protections (COHRP) on behalf of the Component Head as delegated;

 - b. Interface with the Component Head and the Director of the DHA COHRP to report significant issues to the Component Head and to provide guidance to the Director of the COHRP;

 - c. Review, approve, and/or deny institutional Assurances (this responsibility may be delegated to the Director of the DHA COHRP);

 - d. Ensure Continuity of Operations Plan (COOP) is in place and current.

 - e. Identify one regular and one alternate member to represent DHA on the DoD Coordinating Committee for Human Research Protection Programs (CCHRPP); and

 - f. Refer to Reference (e) for additional responsibilities.

3. DIRECTOR, COHRP. Under the authority of the SDO, the Director of the DHA COHRP is the Director of the DHA ORP, who will:
 - a. Establish, manage, maintain, and oversee the daily operations of the DHA HRPP as the Director of the DHA COHRP;

 - b. Set internal policies, procedures, and business processes for the effective and efficient implementation of the HRPP, train the DHA COHRP staff members on those processes, evaluate the effectiveness of processes, and adjust them as necessary to more effectively accomplish goals;

 - c. Develop policies and procedures to execute Reference (e), which implements Part 219 of Reference (f);

 - d. Conduct Assurance establishment and Assurance renewal audits of DHA institutions' HRPPs and approve or deny institutional Assurances on behalf of the SDO;

e. Review and approve each DHA institution's HRPP standard operating procedures (SOP) in addition to local policies and procedures in accordance with guidance from DHA;

f. Conduct routine Site Assistance Visits (SAV) for education, outreach, and guidance and recommend or conduct additional Site Assessment Visits to assess institutional compliance and proficiency with HRPP regulations;

g. Conduct for-cause (FC) audits in response to substantiated noncompliance and other reportable events;

h. Develop educational policy, guidance, and training to be distributed to DHA institutions to support the development and implementation of their institutional HRPP;

i. Per Reference (e), conduct Component Level Administrative Reviews (CLAR) and Human Research Protection Official (HRPO) reviews for DHA institutions, if required;

j. Review and render a decision on submitted justifications for duplicate reviews requested by DHA institutions in accordance with Enclosure 3, paragraphs 2.d., 2.e., and 2.f. of this DHA-AI; and

k. Report to the SDO and DOHRP any:

(1) Unanticipated problems involving risks to subjects or others (UPIRTSO);

(2) Serious or continuing noncompliance with the federal regulations, State and local laws, Native American or Alaskan native tribal laws, foreign laws, DoD issuances and policies, and/or the IRB(s) requirements or determinations;

(3) Suspension or termination of IRB approval; and

(4) Other events or circumstances requiring notifications in accordance with Reference (e) or other DoD or DoD Component policies.

l. Provide to the DOHRP, on behalf of the Component Head and SDO, an index of all DoD-conducted or DoD-supported human subjects research before the end of each fiscal year;

m. Submit requests to waive elements of the Component Management Plan, on behalf of the SDO, to the DOHRP for approval.

4. INSTITUTIONAL OFFICIAL (IO). The IO is required for institutions conducting non-exempt research and is typically the senior-most official at the institution or organization, assigned by the head of the institution or organization, responsible and accountable for the research conducted and/or supported by the institution or organization. IOs will:

- a. Establish, implement, and maintain an HRPP to ensure the institution's compliance with Reference (e) and Part 219 of Reference (f) and this DHA-AI;
- b. Staff and maintain well-qualified HRPP staff along with designating a Human Protections Administrator (HPA)/ Human Protections Director (HPD) as the primary point of contact for the institution's HRPP;
- c. Endorse the DoD institutional Assurance and other appropriate assurances, if applicable;
- d. Provide resources to execute the institution's HRPP, its policies, and SOPs, including but not limited to:
 - (1) Continuing education and training for personnel involved in the HRPP;
 - (2) Meeting space for its own IRB(s) if applicable; and
 - (3) Ensure sufficient staffing to support HRPP functions such as Exemption Determination Official (EDO) reviews, IRB reviews, scientific reviews, record-keeping, and regulatory oversight of research.
- e. Ensure that the institutional HRPP addresses:
 - (1) When and how an investigator will obtain a determination that the newly proposed activity does or does not meet the definitions of "research" and "human subject" in accordance with Reference (e) and Part 219 of Reference (f);
 - (2) When and how an investigator will obtain a determination that the newly proposed research involving human subjects activity does or does not meet the exemption criteria in Part 219, Section 104(d) of Reference (f);
 - (3) Policies and procedures on implementing the regulations and policies referenced on their Assurance, and all other applicable federal regulations, State and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies;
 - (4) Procedures for prompt reporting to the IRB, appropriate institutional administrators, the head of any U.S. Federal department or agency conducting or supporting research, or its designee, and/or the DHA ORP; and
 - (5) Policies and procedures to describe how the institution will monitor, evaluate, and improve the HRPP.
- f. Ensure research at the institution covered by the DoD Assurance and any other appropriate assurances is conducted in compliance with applicable federal regulations, State and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies;

g. Serve as the ultimate authority for human subject research at the institution. The IO may approve or disapprove research involving human subjects to be conducted at the institution in accordance with Part 219, Section 112 of Reference (f);

(1) The IO may not approve research that has been disapproved by the IRB; and

(2) The IO may disapprove research that has been approved by the IRB.

h. Ensure records of each review are maintained in accordance with the COHRP record retention policies, including Enclosure 3, paragraphs 2 and 5;

i. Establish a program of post-approval compliance monitoring of human subjects research that is conducted or supported by the institution;

j. Identify and delegate authority to a(n) Deputy Institutional Official (DIO)/Alternate Institutional Official (AIO), as needed, to maintain appropriate management and oversight. This official must have the authority to enter into agreements and make decisions on behalf of the institution;

k. Complete the appropriate role based, computer-based training and provide copies of the completion certificates to the HPA/HPD for submission to the COHRP;

l. Report any key institutional personnel changes (e.g., HPA/HPD, IRB chair/manager) to the DHA ORP within 5 business days;

m. Maintain institution's federal Assurances, including the DoD Assurance issued by DHA, the Federal-wide Assurance issued by the Department of Health and Human Services (HHS), and any other appropriate Assurances;

n. Provide guidance and oversight to other DHA institutions that rely on the IO's institution and HRPP (e.g., EDO reviews, HRPO reviews, IRB reviews, Assurance coverage);

o. Allow for direct and regular communications with the HPA/HPD for all matters related to the institution's HRPP; and

p. Certain tasks may be delegated down as applicable, but the IO will remain responsible and accountable for the research conducted and/or supported by the institution or organization.

5. DIO/AIO. The IO may formally delegate some or all of their tasks to a(n) DIO/AIO. The role of AIO is defined in Reference (e). For the purposes of DHA and this DHA-AI the role of DIO is equivalent to the Reference (e) role of AIO. Delegation of authority for particular duties does not divest the IO of the responsibility to effectively and efficiently implement and maintain the institution's HRPP. The DIO/AIO can be an active duty member or a civilian government employee. The DIO/AIO will:

- a. Perform the duties and authorities specified in a formal appointment memorandum that is maintained as part of the HRPP records and is made available to the DHA ORP upon request;
 - b. Serve as the Acting IO in the absence of the IO;
 - c. Delegate authorities and responsibilities as needed to another senior official/leader within the institution who has the authority to enter into agreements and make decisions on behalf of the institution. This delegation will be for tasks specified in a formal delegation memorandum and/or consistent with permission to further delegate tasks granted in the DIO/AIO appointment memorandum as per paragraph 6.a. of this enclosure.
6. HPA/HPD. Each institution with an HRPP must have one HPA/HPD who is designated by the IO. The role of HPD is defined in Reference (e). For the purposes of DHA and this DHA-AI the role of HPA is equivalent to the Reference (e) role of HPD. The HPA/HPD will:
- a. Have significant experience in human research protections and serve as a subject matter expert (SME) in the institution's HRPP office;
 - b. Be an active duty member or a civilian government employee;
 - c. Manage the HRPP operations on behalf of the IO including to:
 - (1) Ensure that all institutional HRPP staff have completed all DHA ORP training required for their role;
 - (2) Evaluate the institutional HRPP for compliance, risk, procedural efficiencies, operational redundancies, and resource allocation as part of a continuous quality improvement program;
 - (3) Recommend to the IO appropriately trained and capable individuals to perform EDO and HRPO duties;
 - (4) Maintain all official IRB and IO-level HRPP records for the institution;
 - (5) Report major modifications to the institutional HRPP, including changes to HRPP staff or the COHRP-approved DoD Assurance (e.g., changes to the IO or a request to retire the Assurance), to the COHRP; and
 - (6) Submit reportable items to the DHA ORP, as required, including a summary of the event, supporting documents, and corrective actions, as applicable.
 - d. Serve as an EDO, if trained, to make human subjects research and exempt determinations;

- e. Serve as a HRPO, if trained, to review requests for the institution's support for activities that could include human subjects research in order to ensure compliance with applicable requirements;
- f. Unless delegated the authority by the DHA ORP, submit to the DHA ORP (or their delegate) for approval, prior to initiation, all research that requires CLAR and approval as required by Reference (e);
- g. Maintain records of each review in accordance with DHA ORP record retention policies, including Enclosure 3, paragraph 5;
- h. Investigate allegations and report any substantiated allegations of serious and/or continuing noncompliance, misconduct, undue influence, or coercion regarding research studies to the IO, DHA ORP, and any other regulatory entities (e.g., IRB, Food and Drug Administration in accordance with Parts 50, 56, 312, 600, and 812 of Reference (n)) as applicable;
- i. Participate in ongoing training as directed by the DHA ORP to maintain proficiency or upon issuance of new or revised policy or guidance;
- j. Provide guidance and oversight to other DHA institutions that rely on the HPA/HPD's institution and HRPP (e.g., EDO reviews, HRPO reviews, IRB reviews, Assurance coverage); and
- k. Delegate, as necessary and in writing, the authority to perform specified HPA/HPD duties to appropriately trained and experienced personnel within the institution's HRPP. These authorities cannot be further delegated and any delegate must complete training required to perform each role to be filled before performing such duties.
- l. Ensures key investigators provide an email to the U.S. Central, U.S. Africa, U.S. European, U.S. Indo-Pacific, and U.S. Southern Commands of HSR that is to be conducted or supported in their area of responsibility in accordance with DOHRP guidance. This does not apply to research performed within the United States or DoD institutions overseas.

7. EDO. The EDO will be an active duty member or a civilian government employee appointed to the role, in writing, by the IO. The EDO can be a separate person in the institution or it can be the HPA/HPD trained to perform EDO duties. Contractors supporting the institutional HRPP office may conduct EDO reviews and provide recommendations to a government EDO or the HPA/HPD to make the official determination, as needed. The EDO will:

- a. Have experience in human research protections, serve as an SME in an institutional HRPP, and report to the HPA/HPD;
- b. Determine if an activity constitutes research, if the research involves human subjects, or if the human subjects research is exempt from the requirements in Part 219 of Reference (f);

c. Review research to determine if it needs an approval of an alteration or waiver to a Health Insurance Portability and Accountability Act (HIPAA) Authorization and route the submission to the appropriate Privacy Board or Privacy Office if needed;

d. Notify the principal investigator (PI) and other appropriate individuals (i.e., institutional HPA/HPD) in writing regarding any determinations made;

e. Maintain records of each review in accordance with the HRPP record retention policies discussed in Reference (e) and paragraph 5 of Enclosure 3;

f. Ensure, if applicable, that any additional local administrative requirements are met if an activity has had an EDO review from another institution. If, during a local administrative review, an EDO does not concur with the other institution's determination, the EDO should contact DHA ORP for guidance;

g. Participate in ongoing training as directed by the DHA ORP to maintain proficiency and comply with regulations upon issuance of new or revised policy or guidance; and

h. Coordinate, or if appropriately appointed and trained:

(1) Conduct HRPO reviews of DHA-supported research; and

(2) As a primary or alternate member of an IRB, conduct limited IRB reviews of research for protocols determined to require such review in accordance with Part 219 of Reference (f).

8. HRPO. The HRPO will be an active duty member or a civilian government employee appointed to the role, in writing, by the IO and will conduct reviews of DoD-supported activities in accordance with Reference (e). The HRPO can be a separate person in the institution or they can be the HPA/HPD or EDO trained to perform HRPO duties. Contractors supporting the institutional HRPP office may conduct HRPO reviews and provide recommendations to the government HPA/HPD for concurrence or non-concurrence, as needed. The HRPO will:

a. Have experience in human research protections, serve as an SME in an institutional HRPP office and report to HPA/HPD;

b. Review non-DoD human subjects research activities supported by DoD via contract or comparable agreements and such activities for which DoD provides assistance (see paragraph 3.6.b of Reference (e)) for compliance with DoD-specific requirements;

c. Document the HRPO Review using the tools and resources established per the DHA ORP's and/or the local HRPP's policies and procedures (e.g., HRPO Review Checklist); documentation must be maintained along with the HRPP records specific to that protocol;

d. Maintain records of each review in accordance with the DHA ORP record retention policies including paragraph 5 of Enclosure 3; and

e. Participate in ongoing training as directed by the DHA ORP to maintain proficiency and comply with regulations upon issuance of new or revised policy or guidance.

9. IRB MEMBER. IRB members are active duty members, civilian government employees, or community members nominated for the role by their institution's HPA/HPD and appointed to the role, in writing, by the IO at the IRB's institution. DHA IRBs are established in accordance with the requirements of Reference (e) and Part 219 of Reference (f). IRBs protect the rights and welfare of human subjects participating in research under their purview by reviewing new and ongoing non-exempt research involving human subjects for ethical practices and regulatory compliance. IRB members will:

a. Review research in accordance with Reference (e) and Part 219 of Reference (f), as well as any other applicable requirements (e.g., Parts 50, 56, 312, 600, and 812 of Reference (n)). When the DHA IRB serves as the IRB of record for DHA or DoD-supported research, the IRB review will constitute the HRPO review for the study in accordance with section 3.6.b.(5) of Reference (e);

b. Only approve or vote at a convened meeting to approve research that is in compliance with applicable federal regulations, state and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies and that meets the criteria in Part 219, Section 111 of Reference (f);

c. Complete training prior to conducting reviews, participating in votes at a convened meeting, or counting towards quorum for a convened meeting (see paragraph 4 of Enclosure 3 for more information about required training);

d. Consider the scientific review of proposed research as part of the ethical and regulatory review of the research;

e. Document actions and determinations in meeting minutes in accordance with Part 219, Section 115 of Reference (f) and ensure the meeting minutes reflect a meeting conducted in compliance with the requirements of Reference (e) and Part 219 of Reference (f) and any other applicable requirements;

f. Consult with other committees and individuals (e.g., radiation safety committee, biosafety committee, privacy board, legal office, SME) as appropriate or necessary to ensure a thorough review of submitted research;

g. Ensure expedited reviews are conducted in accordance with Part 219, Section 110 of Reference (f) and are conducted by the IRB Chair or an appropriately qualified IRB member who has been designated as an expedited reviewer by the IRB Chair;

h. As a board, exercise the authority to suspend or terminate approval of research that is not being conducted in accordance with the requirements of applicable regulations or the IRB's requirements, or that has been associated with unexpected serious harm to subjects and promptly report the suspension/termination as well as the reasons for the IRB's action to the investigator(s), appropriate officials at the institution(s) responsible for the research, and the DHA ORP;

i. Review post-approval compliance monitoring reports on non-exempt studies submitted by HRPP staff, evaluate findings, and acknowledge receipt or determine next steps (i.e., to mitigate or investigate findings), as appropriate.

10. PI. The PI of a study is the primary person responsible for the conduct of a research study. Active duty members and civilian government personnel may serve as PIs. Contractors can serve as PIs as long as they are contracted by the institution explicitly to be a PI and the institution where the PI is located allows contractors to be PIs. Contractors who are allowed to be PIs at their institutions must still have a government sponsor for their research. The PI will:

a. Ensure that all protocols are submitted to their local HRPP office for an official determination prior to starting any research via the established web-based protocol management system designated by the DHA ORP;

b. Ensure that all institutionally required reviews and approvals, including but not limited to Office of General Counsel, local Commander, Privacy Office/Board, and Information Management Control Officer are obtained prior to beginning the project;

c. Ensure that all institutionally required agreements, including but not limited to Technology Transfer agreements, Individual Investigator Agreements (IIA), and data sharing agreements are executed prior to beginning the project;

d. Ensure that all research protocols for which they are listed as the PI are conducted in accordance with the written approved protocol, Reference (e), Part 219 of Reference (f), Parts 50, 56, 312, 600, and 812 of Reference (n), and any other applicable federal regulations, state and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies;

e. Ensure that all investigators and study staff associated with the protocol are trained in accordance with DHA ORP policy and conduct the study in accordance with the written approved protocol, Reference (e), Part 219 of Reference (f), and any other applicable federal regulations, state and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies;

f. Ensure that informed consent is obtained from all research participants, unless waived by the IRB, in accordance with Reference (e) and Part 219 of Reference (f), when applicable;

g. Submit any modification to the approved protocol for review and approval prior to implementation. Modifications required to protect the safety of subjects or others may be implemented prior to submission for review and must be submitted to the IRB promptly;

h. Submit continuing review in accordance with Part 219 of Reference (f) and the provisions outlined by the IRB of record, when applicable;

i. Comply with trial and informed consent posting policies in accordance with Part 219 of Reference (f), Parts 50, 56, 312, 600, and 812 of Reference (n), and the Defense Technical Information Center; send a request to the COHRP via the IO for redacting or not posting required documents as needed;

j. Promptly report any reportable events to their IRB of record and local HRPP to be reviewed and forwarded to DHA ORP; and

k. Maintain all study and trial records for the designated time periods in accordance with Reference (e), Part 219 of Reference (f), Parts 50, 56, 312, 600, and 812 of Reference (n), Reference (t), Parts 160, 162, and 164 of Reference (h), and Reference (x), DHA ORP policy, and any other applicable federal regulations, state and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies.

ENCLOSURE 3

PROCEDURES

1. HRPP REQUIREMENTS

a. Establishment of an HRPP

(1) All DHA institutions that conduct, support, or assist human subjects research must maintain an HRPP that includes policies and procedures that are consistent with the requirements defined by Reference (e), Part 219 of Reference (f) and this DHA-AI.

(a) Each HRPP must be approved by DHA ORP prior to implementation. Any changes to HRPP policies and procedures must also be submitted to DHA ORP for approval;

(b) The DHA ORP must be notified of all substantive changes to the HRPP. Substantive changes include changes that:

1. Result in changes in HRPP officials or delegations;
2. Result in new roles and responsibilities for established HRPP Officials;
3. Request/result in establishment of new HRPP positions (while the DHA ORP has no authority over manpower decisions at the institution level, the Director, DHA ORP has a need to know if new positions with regulatory oversight responsibilities are created);
4. Result in changes in scope of authority; and
5. Result in any alteration to the HRPP business processes, policy implementation, or practices.

(2) The institutional HRPP policies and procedures must describe:

(a) Institutional personnel who will be responsible for maintaining the HRPP at the institution and their authorities and responsibilities;

1. All HRPPs conducting non-exempt research must identify an IO, by both name and position, who is typically the senior-most official at the institution or organization and is responsible and accountable for the research conducted and/or supported by the institution or organization; and

2. All HRPPs must identify an HPA/HPD, by both name and position, who serves as the primary HRPP point of contact both for the IO and for the DHA ORP.

(b) The types of research that the institution will allow (e.g., clinical, social-behavioral), and the role of the institution in these research activities (e.g., conducting, supporting, or assisting);

(c) The procedures to identify and ensure that all research involving human subjects conducted, supported, or assisted by the institution meets all DoD requirements detailed in Reference (e) to include procedures that ensure the research receives an ethical and regulatory review by an appropriately trained and authorized DoD official, appropriate to the type of activity being conducted and DoD's involvement in the activity:

1. Activities conducted by the institution or organization that are or may be research involving human subjects must receive a review by an EDO or IRB, as appropriate;

2. Activities conducted by the institution or organization that are non-exempt human subjects research must receive IRB review; and

3. Activities supported by the institution or organization that are or may be research involving human subjects must receive a HRPO review or a DoD IRB review in accordance with section 3.6.b.(5) of Reference (e), as appropriate.

(d) The procedures for appropriate routing of research to ensure protocols receive any required higher-level reviews/approvals (e.g., CLAR, if applicable, DOHRP approval) before work on the protocol may begin;

(e) Procedures for reporting to the DHA ORP findings or allegations of suspensions/terminations, serious or continuing noncompliance and Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) with federal regulations, state and local laws, Native American or Alaskan native tribal laws, foreign laws, and DoD issuances and policies in accordance with Reference (e);

(f) Procedures for post-approval compliance monitoring per each individual DHA institution's HRPP policies and procedures; and

(g) Procedures for review and approval of student research, which is research conducted by a student in pursuit of a degree or as part of a degree program.

(3) A DHA institution that would otherwise require an HRPP under paragraph 1.a.(1) of Enclosure 3, may request HRPP support from another DHA institution's HRPP;

(a) The request for support may be for some (e.g., EDO reviews) or all of the tasks and responsibilities of an HRPP and may or may not include coverage by the supporting institution's DHA-issued Assurance;

(b) The institution requesting HRPP support from another DHA institution must receive DHA ORP approval, in writing, before the institution may conduct HSR;

(c) The requesting institution must identify a point of contact for HRPP-related interactions with the supporting institution and with the DHA ORP.

(4) In addition to the general HRPP requirements, all DHA institutions' HRPP offices should also:

(a) Establish clear lines of communication with the primary HRPP staff and offices at covered or relying institutions; and

(b) Establish procedures for receiving, evaluating, and submitting required reports to the DHA ORP as the COHRP.

(5) Appointment of HRPP Roles and Responsibilities:

(a) Personnel in roles of responsibility associated with research involving human subjects at each DHA institution must be officially appointed to the role by the institution's IO (or DIO/AIO). HRPP Roles and Responsibilities that require IO (or DIO/AIO) appointments include the following, as applicable:

1. Deputy/Alternate IO (DIO/AIO);
2. HPA/HPD;
3. EDO;
4. HRPO; and
5. IRB Members (including any Chairs).

(b) Appointment of HRPP roles and responsibilities must be made in writing:

1. The appointment memorandum must be signed by the IO (or DIO/AIO); and
2. The appointment memorandum should describe the individual's qualifications to assume the role to which they are being appointed.

(c) If an individual will be serving in more than one HRPP role, the appointment memorandum must specifically identify each role and responsibility to which the individual is being appointed, preferably in a single memorandum;

(d) The DHA ORP and the DHA institution's HRPP office, if applicable, should be copied on the appointment memorandum and documentation of the individual's HRPP role-based training;

(e) All HRPP officials involved in the approval of research involving human subjects will:

1. Be DoD employees (i.e., active duty members or federal civilians) sufficiently qualified through appropriate training and experience to ascertain the acceptability of a proposed activity;

2. Be sufficiently removed from the activity to avoid the appearance of a conflict of interest (COI); and

3. Recuse themselves and refer protocols and proposals for review by a different HRPP Official, as necessary, in order to prevent an actual or apparent COI (see paragraph 4.c. of this enclosure).

(f) Current HRPP Officials from institutions transferring into the DHA on/after October 1, 2019, must:

1. Provide the DHA ORP with a copy of all applicable appointment memoranda and, if applicable based on the procedures of the originating Service, all concurrence or delegation memoranda from the Service's COHRP; and

2. Ensure future role-based training is compliant with DHA ORP requirements, conducted by the DHA ORP, or conducted by the institution's HPA/HPD using materials provided by the DHA ORP.

(g) HRPP SOPs:

1. As part of their HRPP, all DHA institutions that conduct, support, or assist research involving human subjects must develop and maintain SOPs that describe the processes and procedures to be followed at the institution in order to maintain compliance with Reference (e), Part 219 of Reference (f) and this DHA-AI;

2. The DHA ORP maintains template SOPs that have been reviewed by the DOHRP and are suitable to the research portfolios of most institutions and IRBs. Deviation from the template SOPs is permitted only with justification to and approval from the Director, DHA ORP;

3. The HRPP SOP must include procedures addressing the institution's use of the web-based protocol management system, in accordance with Paragraph 2(a)(1) of this enclosure, for tracking and documenting all HRPP reviews conducted by the institution;

4. The HPA/HPD of each institution will submit the HRPP SOPs to the DHA ORP for review and approval both initially and prior to implementation of any substantive changes (See paragraph 1.a.(1)(b) of this enclosure for a description of substantive changes). Following DHA ORP approval, the SOPs may be sent to the institution's IO for signature and implementation:

a. If a DHA institution relies on another DHA institution's HRPP office in accordance with paragraph 1.a.(3) of this enclosure, the institution may submit internal SOPs to be included as appendices to the supporting institution's HRPP SOP prior to submission of the supporting institution's HRPP SOP to the DHA ORP; and

b. HRPP SOPs cannot be implemented prior to review and approval by the Director, DHA ORP;

5. Initial SOP review submissions should include:

a. Draft SOP document(s); and

b. Any additional supporting documents that are referenced in the draft SOP document(s) but are not listed among the references herein;

6. SOP update or modification submissions should include:

a. The draft modified SOP document(s), with changes tracked within the document;

b. Any new supporting documents that are referenced in the draft modifications to the SOP document(s) that were not previously approved and are not listed herein; and

c. A full description of any substantive changes to the SOP document(s) (see paragraph 1.a.(1)(b) of this enclosure for a description of substantive changes).

7. Under extraordinary circumstances involving significant risk of harm to the rights, safety, or welfare of human subjects, an institution may implement substantive changes to a previously approved SOP prior to review by the Director, DHA ORP. The Director, DHA ORP must be notified immediately when this occurs and an SOP update or modification should be routed for approval as soon as possible, but not more than 5 business days after the notification;

8. The HPA/HPD, with the assistance of any other HRPP officials and staff members at the institution, is responsible for reviewing and updating the institutional HRPP SOPs as needed. The review of the institutional HRPP SOPs will:

a. Ensure that the SOPs reflect current institutional practices and procedures;

b. Ensure that the SOPs remain in compliance with the requirements of Reference (e), Part 219 of Reference (f), and this DHA-AI; and

c. Be documented in writing and provided to the IO and the DHA ORP upon request.

(h) HRPP Reviews.

1. Initial HRPP Reviews are conducted by the DHA ORP for institutions requesting the establishment of a new HRPP and/or requesting a new DHA ORP issued Assurance;

2. DHA institutions with an HRPP but without an Assurance will receive an HRPP review conducted by the DHA ORP or the DHA ORP's delegate, as necessary;

3. The HRPP Review is intended to evaluate a DHA institution's HRPP in a comprehensive manner. It will include a review of:

a. Training of HRPP personnel;

b. Institutional HRPP policies and procedures for compliance with Reference (e), Part 219 of Reference (f), and this DHA-AI; and

c. HRPP reviews for compliance with Reference (e), Part 219 of Reference (f), this DHA-AI, and the institution's own written policies and procedures.

(i) HRPP Review Procedures.

1. The DHA ORP or the DHA ORP's delegate will notify the institution of the upcoming HRPP Review, including whether the HRPP Review will include a SAV (Assessment or Assistance), in writing. The memorandum will be addressed to the IO and the HPA/HPD will be copied on the correspondence;

2. The notification memorandum will include, as an attachment, a list of requested documents and data to be returned to the DHA ORP or the DHA ORP's delegate;

3. The DHA ORP or the DHA ORP's delegate will work with the HPA/HPD to schedule in-person meetings with the IO (or DIO/AIO), the HPA/HPD, and others with roles, responsibilities, or appointments in support of the local HRPP at the institution that will occur during the HRPP review visit;

4. If time permits during the visit, the DHA ORP or the DHA ORP's delegate will also work with the HPA/HPD to schedule and publicize a town hall meeting with other HRPP stakeholders at the institution (e.g., PIs, research coordinators, other research team members). The purpose of the town hall meeting will be for the stakeholders to listen and understand the functional implementation of the HRPP at the institution;

5. The DHA ORP or the DHA ORP's delegate will issue a written report of the HRPP Review, to include both findings and recommendations for improvement:

a. DHA ORP or the DHA ORP's delegate will communicate tentative (unofficial) findings and trends during an out-brief at the close of the HRPP Review visit. Findings and recommendations are not considered final or official until the report is issued; and

b. It is possible that findings from an HRPP Review will be grave (e.g., noncompliance that is both serious and continuing). If this is the case, DHA ORP will conduct a risk-based (RB) and/or FC audit immediately following the release of the findings.

6. A response to the findings and recommendations identified in the HRPP Review Report in the form of a Corrective Action Plan and/or a Plan of Actions and Milestones must be approved by the IO and submitted by the HPA/HPD to DHA ORP or the DHA ORP's delegate for review and acceptance as required by the report; and

7. The DHA ORP may request support from DHA institutions' HRPP personnel to conduct reviews of other DHA institutions' HRPPs.

(6) All DHA IRBs will be constituted and will function in accordance with Reference (e) and Part 219 of Reference (f). DHA IRBs will follow the IRB SOP template provided by the DHA ORP and will establish, in writing, any necessary local SOPs and policies to supplement the IRB SOP template.

b. Assurances.

(1) Requirements for an Assurance.

(a) Through an Assurance, an institution provides a written commitment to a government agency that it will comply with the requirements in Part 219 of Reference (f); therefore, all DHA institutions that conduct non-exempt research involving human subjects must be covered by a DHA-issued DoD Assurance using the DoD Assurance template;

(b) Regardless of the volume and type of protocols that usually generate from any given DHA institution, each institution that conducts non-exempt human subjects research must be covered either under its own Assurance or be covered under the Assurance of another DHA institution. Researchers at institutions that are not covered by an Assurance who wish to

conduct non-exempt human subjects research must obtain Assurance coverage for their research through IIA(s);

(c) If required, DHA institutions can obtain an Assurance issued by another Federal Agency with the authority to issue Assurances;

(d) All DoD institutions that conduct HHS-funded research must also obtain an HHS Federal-wide Assurance;

(e) Receipt of a non-DoD Assurance does not relieve the DHA institution from the responsibilities set forth in this DHA-AI and applicable subsequent policies, guidance documents, or federal regulations and policies;

(f) The DHA institution must follow the requirements of the Assurances by which it is covered and any reports submitted in accordance with the requirements of a non-DoD Assurance must be simultaneously submitted to DHA ORP; and

(g) If an investigator seeks to conduct non-exempt research and their institution does not hold an Assurance, they may enter into an IIA to associate with an institution that does hold an Assurance in accordance with Reference (e).

(2) Issuance of a DoD Assurance.

(a) Assurances for DHA institutions will be issued by the DHA ORP as the COHRP, (Reference (e)) on behalf of the SDO based in part upon support of the institutional IO or Commander, while also considering:

1. The research mission of the institution;
2. The presence of a Graduate Health Sciences Education program (e.g., Graduate Medical Education Program) and other allied health programs of the Military Services per Reference (1); and
3. The presence of a Clinical Investigation Program (Reference (1)).

(b) DHA institutions conducting or supporting only DoD-funded exempt research involving human subjects, as defined in Reference (e), must maintain an HRPP in accordance with paragraph 1.a. of this enclosure unless there is an agreement in place for HRPP support in accordance with paragraph 1.a.(3) of this enclosure; however, they are not required to obtain and maintain an Assurance;

(c) If an assured (i.e., has an existing Service-specific DoD Assurance) or non-assured DHA institution seeks to conduct non-exempt human subject research and to obtain a DHA-issued DoD Assurance, it must use the current standard DoD Assurance Request template

and submit the request to the DHA ORP for review. The template needs to be completed in its entirety and must include the following:

1. Institution information including all current Assurance numbers (DoD and non-DoD Assurances);

2. Designation of IRBs that may review non-exempt human subjects research conducted by the institution:

a. All IRBs designated in an Assurance must have membership composed in accordance with Part 219 of Reference (f); and

b. Institutional agreements for Institutional Agreement for Institutional Review Board Review (IAIR), or equivalent agreements, for all non-DoD IRBs on which the institution does/will rely must be attached to the DHA Assurance request as an Appendix.

(d) Once an application for a DHA Assurance has been received, the DHA ORP will conduct an initial HRPP Review of the institution's HRPP program and issue an Assurance on behalf of the SDO;

(e) If an institution has a non-conditional HRPP Review, the DHA ORP will issue the institution a DoD Assurance for a period of 5 years;

(f) If an institution has a conditional HRPP Review, DHA ORP can issue the institution a DoD Assurance for a period of less than 5 years (e.g., 6 to 12 months) and DHA ORP will describe the conditions in the DHA Assurance issuance memorandum:

1. Institutions that meet all conditions before the end of the Assurance period will be issued an unconditional Assurance; and

2. The DHA ORP will determine whether to issue the unconditional Assurance for the remainder of the original Assurance period or to issue a standard, unconditional 5-year Assurance when an institution has met all conditions.

(3) Assurance Renewals.

(a) Assurance Renewal Audits. All DHA ORP audits are subject to the requirements of Reference (e):

1. If the DHA institution has been issued a DoD Assurance by the DHA ORP for a period of 5 years, an Assurance renewal audit will be conducted no later than the final 3 to 9 months of the standard 5-year Assurance cycle to evaluate the DHA institution's HRPP policies and procedures (Note: An extension may be granted by the Director or ORP or it may be

conducted earlier than the last year) and, if applicable, its progress in resolving any conditional issues identified from a previous assessment or assistance visit;

2. If the DHA institution has been issued a DoD Assurance by the DHA ORP for a period of less than 5 years, the Assurance renewal audit of the DHA institution's HRPP will be conducted no later than 90 days prior to expiration unless an extension is given; and

3. DHA ORP will provide the DHA institution with specific tasks and responsibilities to accomplish prior to, during, and after the DHA ORP Assurance Audit.

(b) SAV. (Site Assessment and/or Assistance Visits)

1. SAVs are a type of HRPP Review conducted to evaluate the institution's HRPP policies and procedures and, if applicable, its progress in resolving issues from a previous Assurance Audit or a previous SAV:

2. If the DHA institution has been issued a DoD Assurance by the DHA ORP for a period of 5 years, a SAV will typically be conducted in the third year of the standard 5-year Assurance cycle to evaluate the DHA institution's HRPP (it may be conducted earlier) and, if applicable, its progress in resolving any conditional issues identified from a previous DHA Assurance Audit or a previous SAV;

3. If the DHA institution has been issued a DoD Assurance by the DHA ORP for a period of less than 5 years, an interim SAV of the DHA institution's HRPP will typically be conducted in the middle third of the approved Assurance period (e.g., at 3-4 months for a 6-month approved Assurance; or at 4-8 months for a 12-month approved Assurance); and

4. DHA institutions may request additional SAVs, as needed, to evaluate their HRPP.

(4) RB and FC Audits

(a) The DHA ORP has the authority to conduct RB and/or FC Audits of any DHA ORP-approved HRPP;

(b) DHA ORP may request support from DHA institutions' HRPP personnel and other DoD Components, federal agencies, etc., as appropriate to conduct audits of other DHA institutions' HRPPs;

(c) In the case of a FC Audit, the identified cause will determine the audit's scope. The scope of the audit may include the entire HRPP at the DHA institution or only a component thereof (e.g., the IRB, selected DHA-conducted protocols, selected DHA-supported protocols); and

(d) RB and FC Audits will generally follow the procedures identified in paragraph 1.a.(5)(i) of this enclosure with the following additions and revisions:

1. DHA or DHA's delegate will give the institution no less than 5 business days' written notice of the Audit;

2. The reason for the audit (i.e., RB or FC) will be disclosed to the institution with the written notification of the audit. If the audit is FC, the institution will be notified of the cause in a manner that preserves the integrity of the audit;

3. DHA or DHA's delegate will work with the HPA/HPD to schedule appropriate meetings with HRPP officials in accordance with the scope of the audit; and

4. All RB and FC audits will include an out-brief to the IO at the conclusion of the in-person visit.

(5) Revoked, Suspended, or Terminated Assurances. During the life of an issued Assurance, the DHA ORP has the authority to:

(a) Impose new or additional conditions on the Assurance if the DHA ORP determines that cause exists for such action;

(b) Revoke, suspend, or terminate the Assurance if the DHA ORP determines that cause exists for such action; and

(c) Retire the Assurance if the DHA ORP determines that the Assurance is no longer needed.

c. Collaborating with Non-Assured Institutions

(1) DHA institutions that hold Assurances may identify a need to conduct collaborative research with institutions that do not hold an Assurance issued by a federal agency;

(2) This is permissible in the following circumstances:

(a) All investigators engaged in the conduct of non-exempt human subjects research, in accordance with Reference (e), must be covered by an Assurance;

(b) An Assured institution may extend their Assurance to cover investigators who are employees or agents of a non-Assured institution only through the use of an IIA;

(c) Assured DHA institutions may use the DoD template IIA without approval from the Director, DHA ORP;

(d) Investigators at non-Assured DHA institutions may, with the approval of their IO/Director/Commander, enter into an IIA with an Assured institution in order to conduct non-exempt human subject research;

(e) The scope of an IIA may include all research performed by an individual in collaboration with the Assured institution or may be limited to a specific protocol or set of projects; and

(f) An IIA needs to be executed for each research team who will perform activities that constitute engagement in non-exempt research involving human subjects.

d. DoD-Affiliated Personnel Participation in Research. DoD-affiliated personnel may be subjects in research; however, Reference (e) includes additional protections for these subjects. They include:

(1) Subjects must be notified if the research includes any risks to their fitness for duty, and instructed to seek command guidance for approval for research participation;

(2) Active duty members and civilian supervisors, officers, and others in the chain of command are prohibited from influencing their subordinates' decisions to participate in research involving human subjects and being present during recruitment of subordinate DoD personnel. Supervisory/senior personnel may be recruited into studies at separate recruitment events; and

(3) An IRB approved ombudsman must be present during group recruitment of DoD personnel into greater than minimal risk research, and must have policies/procedures IAW Reference (e) for DOD-affiliated personnel.

e. Privacy. DHA-specific requirements to protect the privacy and confidentiality of subjects are located in Parts 160, 162, and 164 of Reference (h) and include:

(1) In accordance with Reference (e), DHA-conducted, -supported, or -assisted research involving large-scale genomic data (LSGD) collection from DoD personnel must include an HHS Certificate of Confidentiality (CoC) (Reference (w)) and must be submitted to the DHA ORP for a security review to ensure adequacy of the proposed administrative, technical, and physical safeguards. DHA ORP will then send to DOHRP for approval as required. Use of CoCs must be in accordance with Reference (am) and guidance from the DOHRP;

(2) The DHA adheres to the policies in Parts 160, 162 and 164 of Reference (h), which includes protections for the use and disclosure of protected health information in research;

(3) The appropriate DHA IRB or privacy board will review all protocols within its purview that are subject to HIPAA for compliance with the regulatory requirements of Parts 160, 162, and 164 of Reference (h). Some privacy boards may also require a separate review for

certain studies as described in their local SOPs (e.g., genomic studies with non-DoD collaborators);

(4) In accordance with Reference (x), DHA investigators proposing to use DHA-managed data may need to obtain a Data Use Agreement or Data Sharing Agreement from the DHA Privacy and Civil Liberties Office. This is a separate review which can be required even after IRB approval to re-approve or verify that the privacy portion of the review was executed correctly;

(5) Unless a waiver or alteration request is approved by the IRB/privacy board, a signed Authorization for the Use and Disclosure of Protected Health Information (i.e., HIPAA Authorization) will be obtained from each subject prior to such use or disclosure for research purposes; and

(6) DHA institutions will maintain procedures to ensure the protection of subjects' sensitive information that is collected for research as described in Reference (e). These include:

(a) DHA institutions may use the authority pursuant to Title V, Section 502 of Reference (i) to assure that data or information acquired by the DHA under a pledge of confidentiality for exclusively statistical purposes may not be disclosed in identifiable form for any other purposes, except with the informed consent of the respondent;

(b) DHA institutions conducting, supporting, or assisting research involving human subjects may apply for an HHS CoC in accordance with Reference (w). If issued a CoC, the research institution is expected to implement the privacy protections offered by the CoC, regardless of the person's civilian or active duty members status;

(c) A CoC prohibits disclosing or providing, in any federal, state, or local civil, criminal, administrative, or other proceeding, or to any other person not connected with the research, the name of any individual or any such information, document, or biospecimen that contains identifiable information about the individual, created or compiled for purposes of research. This also includes any forced disclosures, including those that are subject to the Uniform Code of Military Justice or the Military Rule of Evidence; and

(d) Exceptions to the CoC must be listed in all informed consent documents, pursuant to Reference (e) and Part 219 of Reference (f).

2. RESEARCH SUBMISSIONS.

a. 2018 Requirements of Part 219 of Reference (f).

(1) Protocols reviewed and approved prior to 20 January 2019 were reviewed in accordance with the Pre-2018 Requirements of Part 219 of Reference (f). With the approval of

the IRB or the HRPP Official responsible for oversight, these studies may be/may have been transitioned to the 2018 Requirements of Part 219 of Reference (f). All new protocols reviewed and approved on or after 20 January 2019 are automatically reviewed in accordance with and subject to the 2018 Requirements of Part 219 of Reference (f).

(2) While the language in paragraph 2 of this enclosure refers predominately to the 2018 Requirements of Part 219 of Reference (f), it should be understood that some research conducted, supported, and/or assisted by DHA institutions remains subject to the Pre-2018 Requirements of Part 219 of Reference (f).

b. Use of a Web-based Protocol Management System

(1) All DHA institutions are required to use the designated Military Health System-wide, web-based protocol management system for workflow processing of both DoD-conducted and DoD-supported research involving human subjects, in accordance with Reference (al). This requirement extends to activities conducted with external collaborators. The requirement for using the web-based protocol management system encompasses protocol submissions for HRPP reviews (both initial reviews and life-cycle actions), routing of submissions among DHA institutions (e.g., routing a non-exempt protocol from a site without an IRB to a site with an IRB for review), and routing submissions from DHA institutions to DHA ORP for any required COHRP-level review (e.g., any protocols that require DOHRP approval prior to start, certain reportable events);

(2) Any existing protocols for DoD-conducted or DoD-supported research that are not currently in the web-based protocol management system (e.g., protocols that were approved before April 25, 2016) must be entered into the system no later than the time of their next life-cycle action (e.g., modification, continuing review, annual report);

(3) E-mail submissions will only be accepted in the event the web-based protocol management system is unavailable. Once the web-based protocol management system is again available, the investigator will be asked to submit the documents in the system and the submission will be reviewed and completed in the web-based protocol management system; and

(4) All DHA institutions are encouraged to develop thorough record-keeping processes, including the tracking and maintenance of physical records, if feasible, in their HRPPs that will memorialize local research activities and enable continuity of operations and ease of reporting.

c. Preliminary Review. DoD personnel who plan to conduct activities that require an HRPP review must submit their protocol/proposal to their institution's HRPP office via the web-based protocol management system for a preliminary review. The HPA/HPD or HRPP staff at the institution will route the submission to the appropriate official or board for formal HRPP review.

d. Single Institutional Review Board (sIRB) Reviews

(1) Reference (e) and Part 219 of Reference (f) require minimization of the number of IRBs that review and approve research, and justification for any duplication of review;

(2) As part of the effort to improve the efficiency of IRB review(s) for collaborative and multi-site research projects, DHA IRBs may serve as a sIRB in support of multi-institutional collaborative or multi-site research projects as a performance site, lead site, and/or coordinating center. IAIRs are not required between DoD institutions relying on another DoD IRB as both rely on DoD Assurances. When a DHA IRB serves as the sIRB for DoD-supported research, the IRB review will constitute the HRPO review and an additional HRPO review is not required, in accordance with section 3.6.b.(5) of Reference (e);

(3) Requests for additional HRPP regulatory reviews of protocols that have previously received an HRPP regulatory review (e.g., EDO, IRB, HRPO reviews) must be submitted, with justification, to the DHA ORP in writing before the additional/subsequent/duplicative review is conducted. The DHA ORP will consider these requests on a case-by-case basis:

(a) DHA ORP approval is not required to conduct reviews of protocols going through standard HRPP review processes (e.g., IRB review following an EDO determination of non-exempt human subjects research, or HRPO review of a DoD-supported study that has received non-DoD IRB review/approval) and is not required to conduct administrative reviews of protocols reviewed by a different DoD HRPP in order to ensure that all local requirements are satisfied; and

(b) DHA ORP approval is required prior to conducting any HRPP review that could be considered duplicative (e.g., IRB review of a protocol that has already been approved by a different IRB, HRPO, or EDO review of a protocol that has already received a determination from a HRPO/EDO at a different institution or with a different Component).

e. Determinations.

(1) Not Research (NR) and Research Not Involving Human Subjects (RNIHS).

(a) All proposed activities that could meet the definition of “research” involving “human subjects”, in accordance with Reference (e) and Part 219 of Reference (f), must be reviewed by an EDO for a determination following submission of a proposal using the web-based protocol management system and prior to the commencement of the proposed activities;

1. EDOs will assign a determination of NR to proposed activities that do not meet the definition of “research” found at Part 219, Section 102(l) of Reference (f) and a determination of RNIHS to proposed activities that do meet the definition of “research” found at Part 219, Section 102(l) of Reference (f) and do not meet the definition of “human subject” found at Part 219, Section 102(e)(1) of Reference (f). Proposed activities that meet both definitions are considered to be “research involving human subjects” or “human subjects research” and will be considered for an exemption determination:

a. Part 219 of Reference (f) identifies four types of activities that are, by definition, not considered to be research. Proposed activities that may fit into one of these excluded categories must be reviewed by an EDO for a determination prior to the commencement of the proposed activities. Activities that fit the description of one of these excluded categories should receive a determination of NR; and

b. Reference (e) identifies six types of activities commonly conducted or supported by DoD institutions that are not considered to be human subjects research. Proposed activities that may fit into one of these excluded categories must be reviewed by an EDO for a determination prior to the commencement of the proposed activities. Activities that fit the description of one of these excluded categories should receive a determination of NR or RNIHS, as appropriate.

2. Protocols that receive an NR or RNIHS determination are not required to adhere to the protections of Part 219 of Reference (f);

(a) If any modifications are made to the protocol that may change the determination to research involving human subjects, the protocol must be submitted again for review via the web-based protocol management system; and

(b) If the research protocol will be conducted at multiple DoD institutions, the protocol and the original EDO review and determination can be submitted to each subsequent institution for an administrative review to ensure that the protocol complies with local requirements; however, the single EDO review is sufficient and the EDO review must not be duplicated.

(2) Exempt Research Involving Human Subjects

(a) Part 219, Section 104(d) of Reference (f) lists human subjects research activities that are exempt from some or all of the requirements of Part 219 of Reference (f). These activities must, however, comply with References (e) and (m), this DHA-AI, and the requirements of Part 219 of Reference (f) as specified in each exempt category;

(b) If an investigator believes their research protocol qualifies for one of the exemption categories, they must submit the research protocol to their DHA institution's EDO for a determination using the web-based protocol management system;

(c) Broad consent is permitted in DoD-supported research in accordance with Reference (e) and Part 219 of Reference (f);

(d) If the research protocol will be conducted at multiple DoD institutions, the protocol and the original EDO review and determination can be submitted to each subsequent institution for an administrative review to ensure that the protocol complies with local

requirements; however, the single EDO review is sufficient and the EDO review must not be duplicated;

(e) Protocols that receive a determination of exempt research involving human subjects are not required to adhere to the protections of Part 219 of Reference (f), but must still comply with all applicable DoD-specific requirements identified in Reference (e); and

(f) If a research protocol receives an exempt determination of category (2)(iii), category (3)(i)(C), category 7, or category 8, it will be routed for limited IRB Review:

1. The limited IRB review may be conducted via expedited review procedures per Part 219 of Reference (f) and will be conducted in accordance with the requirements of Part 219, Section 111(a)(7) or Part 219, Section 111(a)(8) of Reference (f), as identified in the assigned exemption category; and

2. The limited IRB review must be conducted by an IRB or designated IRB member. EDOs generally do not have the authority to conduct IRB reviews, including the limited IRB reviews required by exempt categories 2, 3, 7 and 8. An EDO may conduct limited IRB reviews if and only if they have been appointed as a member of an IRB and have been delegated the authority to conduct expedited IRB reviews.

f. Non-exempt Research Involving Human Subjects.

(1) A protocol will be routed for IRB review if an EDO determines that the protocol is human subjects research that is not exempt from the requirements of Part 219 of Reference (f);

(2) Prior to or immediately following IRB review, the protocol must receive any required ancillary reviews such as reviews by the Institutional Biosafety Committee or the Radiation Safety Committee. Obtaining such reviews is the responsibility of the PI and the reviews shall be conducted in accordance with the DHA institutions' local policies and procedures;

(3) Non-exempt research protocols must receive a review of their scientific merit in accordance with Reference (e). Detailed requirements for consideration of scientific reviews can be found in paragraph 3.a.(4) of this enclosure and Reference (ak);

(4) In accordance with Reference (ad), research protocols that will utilize recombinant or synthetic nucleic acid molecules must be reviewed by the Institutional Biosafety Committee to determine if a comprehensive risk mitigation plan is in place to protect the researchers as well as the human research subjects;

(5) Research protocols that require additional radiologic procedures as a part of the research (i.e., radiation procedures that are not standard of care) may need to be reviewed by a radiation safety committee to determine if the risks from the additional radiation procedures in

human subjects are necessary to carry out the goals of the research and have been adequately communicated to subjects in the informed consent form;

(6) Research protocols that require legal reviews may have these performed concurrently with the HRPP regulatory review;

(7) Classified research conducted by DHA personnel must be approved by the DOHRP in accordance with Reference (e); therefore, all proposals that intend to include classified activities must be submitted to the DHA ORP for routing to the DOHRP. Institutional HRPP staff should contact the DHA ORP for instructions to securely submit any classified research that requires a CLAR or for which they need other DHA ORP assistance;

(8) All DoD funded research involving a human being as an experimental subject must comply with Section 980 of Reference (d) and Reference (e). Non-exempt research protocols requesting a waiver or alteration of informed consent must be evaluated to determine whether they meet the Reference (e) definition of “research involving a human being as an experimental subject.” Request for the waiver must be submitted to DHA ORP for review and will be forward to OUSD(R&E) for approval;

(9) In accordance with Reference (e), subjects injured in DoD-conducted research may obtain care for such injuries at a MTF on a space-available basis during the pendency of the research study in accordance with Reference (af);

(10) DoD conducted research determined to be greater than minimal risk must provide subjects with an explanation as to whether any compensation and any medical treatments are available for research-related injuries as part of the informed consent process. These explanations must include, but should not be limited to: a statement that subjects may, for the duration of the study, be eligible for healthcare services for research-related injuries at an MTF, in accordance with Part 108 of Reference (f) and Reference (an) and a statement that this eligibility for healthcare services extends beyond subjects’ participation in the study to such time after the study has ended, in accordance with Part 108 of References (f) and Reference (an); and

(11) DoD supported research must follow Part 219 of Reference (f) and requirements as defined in Reference (e).

(12) If the research protocol will be conducted at multiple DoD institutions, following IRB approval of the core protocol, each additional participating site must complete a site-specific application for review by the local HRPP and the IRB before the research can begin at the site. As part of this process, the protocol and the original IRB review and approval can be submitted to each subsequent institution for an administrative review to ensure that the protocol complies with local requirements; however, the single IRB review is sufficient and the IRB review must not be duplicated.

g. Reportable Events.

(1) The PI conducting non-exempt research is responsible for reporting the events identified in this section to the IRB of Record. If a reportable event occurs in DoD conducted exempt research or any DoD-supported research, the PI is responsible for reporting the event to the DoD institution's HRPP office, and HRPO if applicable, using the web-based protocol management system;

(2) The HPA/HPD at the DHA institution is responsible for reporting events, as required in this section, to the IO and the DHA ORP. The HPA/HPD is also responsible for coordinating with the PI to ensure appropriate notification is made to the HRPP office at any sites participating in multi-site research:

(a) Depending on the nature of the event and the nature of the research in which the event occurred, there may be reporting requirements (e.g., HIPAA, Information Technology security, Food and Drug Administration) in addition to those addressed herein. Knowing and adhering to these requirements is the responsibility of the PI; and

(b) For the purpose of this DHA-AI, "promptly" is defined as within 3 business days from the time when a member of the research team becomes aware of the event, when the IRB or HRPP receives a report from the PI, and when DHA ORP receives a final report from the HPA/HPD.

(3) AEs. An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporarily associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (Reference (ai), as modified by Reference (aj)). AEs must be reported to the IRB, the HRPP office and/or the DHA ORP, when applicable per below:

(a) Both Unexpected and Unrelated AEs.

1. These are events that could not have been predicted and for which there is no reasonable possibility that the event could have been caused by the procedures involved in the research; and

2. There is no requirement for PIs to report these events to the IRB or the HRPP office.

(b) Expected and related/possibly related AEs.

1. These are predictable events that are or could have been caused by the procedures involved in the research or are anticipated given the subject population or condition being studied. Anticipation of such occurrences should have been addressed in the research protocol and disclosed to potential subjects during the informed consent process; and

2. PIs must report these events in aggregate to the IRB and the HRPP office at the time of the continuing review. These events do not need to be reported to the DHA ORP.

(c) Unexpected and related/possibly related AEs.

1. Events that could not have been predicted, but are or could have been caused by the procedures involved in the research, and places subjects or others at increased the risk;

2. PIs must report these events promptly to the IRB and the HRPP office; the HPA/HPD must promptly report the events to the DHA ORP.

(4) Noncompliance. The failure of a person, group, or institution to act in accordance with Reference (e), its references, or applicable requirements (see the Glossary of Reference (e)).

(a) Continuing Noncompliance is a pattern of noncompliance that suggests the likelihood that, without intervention, instances of noncompliance will recur. It can also be a repeated unwillingness to comply with Reference (e) or a persistent lack of knowledge of how to comply with Reference (e);

(b) Serious Noncompliance is the failure of a person, group, or institution to act in accordance with Reference (e) 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;

(c) Any individual who witnesses apparent noncompliance is responsible for reporting the noncompliance to an oversight authority (e.g., the PI, the IRB, the HPA/HPD);

(d) Upon receipt of an allegation of noncompliance, the IRB must coordinate with the HPA/HPD to ensure timely and accurate reporting. The investigative body for allegations of noncompliance (usually the IRB, but sometimes the HPA/HPD or another appropriate official (IO or designee)) must have appropriate processes in place to properly investigate the allegation, determine whether the allegation is substantiated, determine whether a substantiated report of noncompliance constitutes serious and/or continuing noncompliance, and develop an action plan for resolving the situation and, if appropriate, submit a recommendation to the IO for corrective/remedial action;

(e) The HPA/HPD must promptly notify the IO and the DHA ORP when a substantiated allegation of noncompliance is received; and

(f) The HPA/HPD must provide interim reports to the IO and the DHA ORP during the investigation and a final report within 5 business days of a determination of serious or continuing noncompliance.

(5) UPIRTSOs.

(a) While all unexpected and related/possibly related AEs that increase risk to subjects are UPIRTSOs, not all UPIRTSOs are AEs because UPIRTSOs include incidents or outcomes that may not be directly experienced by subjects. A UPIRTSO is any incident, experience, or outcome that meets ALL three of the following conditions:

1. 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;

2. 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); and

3. 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.

(b) All UPIRTSOs must be reported promptly to/through the HRPP oversight chain of command (i.e., the PI reports to the IRB/HRPP Official, the HPA/HPD reports to the IO and DHA ORP, DHA ORP reports to DOHRP). If the UPIRTSO is a research subject death, however, that reporting window is reduced from "promptly" to within 24 hours of notification or awareness of the event, across the HRPP oversight chain of command;

(c) Upon receipt of the report of an unexpected and related/possibly related AE or a comparable incident/outcome, the IRB must review the event/incident/outcome and determine whether it meets the definition of a UPIRTSO, determine whether the PI's proposed action plan for resolving the situation is adequate and appropriate, and, if necessary, work with the PI to develop a more appropriate action plan. In addition, reviews and determinations must be documented in meeting minutes and include a justification for the determination made. The PI must be notified of the determination in writing, and the HPA/HPD must be informed. Upon receipt of the determination, the HPA/HPD will draft and submit any required additional reports to the DHA ORP;

(d) The HPA/HPD must provide interim reports to the IO and the DHA ORP every 30 days, or upon request, if the IRB has not yet made final determinations within the 30 days;

(e) The HPA/HPD must provide a final report to the appropriate Federal Agency (FDA and/or OHRP), if applicable, IO and DHA ORP within 5 business days of receiving the IRB's final determination;

(f) Upon receipt of an initial/interim/final report of a UPIRTSO, serious noncompliance, or continuing noncompliance from an institution's HPA/HPD, the DHA ORP will also promptly notify the DOHRP for additional reporting, as required; and

(g) Upon receipt of a final report of a UPIRTSO or of serious or continuing noncompliance, DHA ORP will promptly notify the DHA SDO, the Director, DHA, and the DOHRP.

3. THE ROLE OF THE DoD IN THE RESEARCH

a. DoD-Conducted Research.

(1) CLAR.

(a) Per Reference (e), CLARs are required for all non-exempt human subjects research under the following conditions:

1. The research is being conducted in a foreign country unless the research will be conducted by an established DoD overseas research institution in the host country, or the research will be conducted by a DoD overseas institution and will include only DoD personnel or US citizens as subjects;

2. The research requires waiver of informed consent under Section 980 of Reference (d);

3. The research intends to collect LSGD from DoD personnel;

4. The research involves fetuses or fetal tissue;

5. The research requires approval by the DOHRP; and

6. The research is classified human subjects research.

(b) Per Reference (e), CLARs and security reviews are both required before research involving LSGD collected from DoD personnel may begin; and

(c) The DHA ORP may, with DOHRP approval, delegate CLARs and oversight to a DHA institution.

(2) As stated in paragraph 2.d. of this enclosure, requests for review of non-exempt research involving human subjects by more than one IRB must be approved in writing by the DHA ORP in advance of the subsequent review;

(3) DHA institutions that will rely on non-DoD IRBs or HRPPs for any of their regulatory reviews must have procedures to ensure that the described activity is compliant with DoD-specific requirements in accordance with Reference (e);

(4) Scientific Review.

(a) DHA institutions conducting non-exempt research involving human subjects must have procedures established to ensure that a scientific review of proposed research is conducted and that the scientific review is considered by the IRB during its deliberations;

(b) If the IRB of record is a non-DoD IRB, the DHA institution must obtain written affirmation from the institution providing the IRB services that the IRB did/will consider the scientific merit of the proposed research during its deliberations prior to executing an IAIR;

(c) In accordance with Reference (e), DHA IRBs may document their own or a non-DoD IRB's consideration of scientific merit according to the DHA institution's HRPP policies and procedures. These policies and procedures must include a mechanism and conditions by which they will accept other documentation that verifies scientific merit review from a non-DoD institution (e.g., documentation of scientific review and approval noted within the IRB approval memorandum; a separate scientific review approval hard copy, scan, or electronic communication); and

(d) The DHA ORP has determined the National Cancer Institute (NCI) Central IRB's rigorous scientific review process meets the Reference (e) requirement for IRB consideration of scientific merit and feasibility of study completion; protocols conducted or supported by DHA institutions that include an NCI collaborator and/or are under the NCI Central IRB's purview, therefore, do not require additional (local) scientific review or documentation of IRB consideration.

b. DoD-Supported Research.

(1) All contracts and solicitations for DoD-supported research that include or may include research involving human subjects must contain the clause (i.e., Defense Federal Acquisition Regulation Supplement Clause) found in Parts 252.235-7004 of Reference (y) in its entirety in accordance with Part 252.072(e) of Reference (y). Comparable agreements (e.g., grants, assistance agreements, Cooperative Research and Development Agreements) that include or may include research involving human subjects but are not subject to Parts 252.235-7004 of Reference (y) must state the responsibilities of the non-DoD institution. The requirement for HRPO review does not apply if the non-DoD institution is a Federal Department or agency that has adopted Part 219 of Reference (f);

(2) The DHA institution supporting the project must provide their HRPO's contact information and/or instructions for submission to the non-DoD institution so that the DHA

institution can conduct a HRPO review of the study in accordance with Reference (e) and Parts 252.235-7004 of Reference (y);

(3) Following IRB or HRPP regulatory review, the non-DoD institution must submit the approved project to the supporting DHA institution using the web-based protocol management system (Note, only one HRPO review is required);

(4) The HRPO must concur with the non-DoD determination before the research may commence; and

(5) If a DoD IRB serves as the single reviewing IRB of record under Part 219, Section 114 of Reference (f), the DoD IRB approval will constitute the HRPO review and no additional documentation of HRPO review is required.

c. DoD-Assisted Research.

(1) DoD-assisted research is research for which DoD provides non-financial resources to non-DoD institution(s) conducting research. These resources may include, but are not limited to, facilities, equipment, access to information about DoD-affiliated personnel for recruitment, direct access to DoD-affiliated personnel, data, and specimens;

(2) DHA institutions may provide assistance for research at the discretion of the IO (or DIO/AIO) on a case-by-case basis or in accordance with institutional policy; and

(3) DHA institutions that assist with research must have a process through which staff at the DHA institution can conduct an administrative review of requests for assistance to ensure that the DHA institution is not engaged in the research and that all applicable local and DoD requirements are met (e.g., additional protections for DoD-affiliated personnel).

4. PERSONNEL, TRAINING, COI REQUIREMENTS.

a. Personnel. Contract personnel may serve as the PI in DoD conducted, supported, or assisted research, provided that another active duty member or DoD employee is listed as an investigator on the study or as the study's Government Project Manager or point of contact.

(1) DHA institutions are not precluded from limiting PI roles and responsibilities to full-time government staff members, either civilian or active duty members, officially assigned to the DHA institution as local policy;

(2) If local policy allows for contract personnel to serve as the PI in DoD-conducted, -supported, or -assisted research:

(a) It is recommended that the contract language explicitly addresses the roles and responsibilities and expectations of the contract PI; or

(b) At a minimum, the contract PI is credentialed/privileged or otherwise authorized to work at the institution where they are doing the research.

(3) Research protocols must identify the PI, research study coordinator, and all other key study personnel. The role(s) and responsibilities of each key study personnel member must be identified in the protocol.

b. Training.

(1) The DHA ORP shall ensure that all HRPP oversight personnel, including the IOs, DIO/AIOs, HPA/HPDs, EDOs, HRPOs, IRB members, HRPP, and IRB support staff members and other officials providing HRPP oversight services, receive initial and continuing human subjects protection training commensurate with their duties and responsibilities, as set forth by Under Secretary of Defense for Research and Engineering standards;

(2) Per Reference (k), all personnel associated with research involving human subjects, including all investigators, research staff members, HRPP oversight personnel, members of the IRB, etc., must provide documentation of successful completion of role-based training and education in accordance with Reference (e); training documentation will be subject to institutional and DHA ORP audit. A DHA IRB cannot approve a study and DHA EDOs cannot release a determination until all investigators have completed their human subject protection training;

(3) DHA ORP role-specific training for IOs, DIOs/AIOs, HPDs/HPAs, EDOs and HRPOs needs to be completed as required within 3 months of assuming the position. DHA ORP role/review-specific training must be renewed not less than every 3 years for an individual to retain their specific role authority.

(4) DHA ORP has established computer-based training, available via the COHRP-identified program, which meets the role-specific requirements of References (e) and (k). This training is available to all DHA HRPP personnel. DHA ORP is responsible for ensuring that this training is up-to-date with current federal regulations, DoD-wide policies, and any other applicable policies;

(5) In accordance with Reference (k), comprehensive, role-based training is required every 3 years. Renewal of the computer-based training satisfies this requirement; and

(6) In accordance with References (k), interim or refresher training is required for all DoD personnel on an annual basis.

c. COIs.

(1) General Requirements

(a) Each PI, research study coordinator, and all other key study personnel members must attest to being free of any and all COIs, real or apparent, and that attestation must be included with a written submission for review. If not free of COIs any COIs, real or apparent, that are noted must be evaluated during the initial review. Any new COIs, real or apparent, must be submitted to the IRB or other regulatory reviewing official who is responsible for the continuing/ongoing oversight of the activity within 3 business days of the COI becoming evident to the affected individual;

(b) Disclosure and management of COIs apply to IRB members and support staff as well. Local HRPPs must have policies and procedures for identifying and managing COIs within the IRB and support staff;

(2) Identification of COIs: Financial/Professional/Familial/Others

(a) Financial Interests. Financial interests can conflict with the interests of protecting human subjects for both investigators and reviewers. The categories and criteria below should be understood to apply to both investigators and reviewers.

1. An individual has a significant financial interest with respect to a protocol when the individual or their immediate family receive, in aggregate, any of the following over a 12-month period:

- a. Compensation that could be affected by the study outcome;
- b. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright, or licensing agreement, or the right to receive royalties from product commercialization;
- c. Any equity interest in the sponsor or product of value that cannot be readily determined through preference to public prices (e.g., ownership interest or stock options);
- d. Any equity interest in the sponsor or product that exceeds \$10,000 or 5 percent ownership interest;
- e. Significant payments or other sorts of compensation with a cumulative value of \$10,000 made directly by the sponsor as an unrestricted research or educational grant, equipment, consultation, honorarium, or other payment; and

2. The following are not considered a significant financial interest:

a. Salary, royalties, or other compensation paid by the institution employing the investigator to the investigator, research support staff, or IRB members; and

b. Income from service or advisory committees or review panels for federal, state, or local government agencies.

(b) Professional Interests. Professional interests can conflict with the interests of protecting human subjects for both investigators and reviewers.

1. Investigators may experience institutional or other professional pressure to publish the findings of their research or otherwise prioritize outcomes over the protection of human subjects;

2. Reviewers may experience actual or perceived pressure to approve particular research because the topic is of interest to leadership; because the investigator is a supervisor, subordinate, or high ranking official; or for other reasons; and

3. Investigators or researchers who perform multiple institutional roles, such as an investigator who conducts research, and is also a practicing clinician and an academic lecturer, may not be able to devote sufficient time to ensure the protection of human subjects in their research.

(c) Familial Interests. Outside of the financial interests of family members identified, it is uncommon for investigators to encounter familial interests that conflict with the interests of protecting human subjects. Familial interests that do or may conflict with the interests of protecting human subjects are more common for reviewers who might, for example, be asked to review a protocol on which their spouse is an investigator; and

(d) Other Interests. The types of interests that drive individuals to act are not limited to the categories described above. Interests and motivations are infinitely variable and consideration of COIs should not be limited to conflicts among the interests explicitly described herein.

(3) Management.

(a) DHA institutions will establish, as part of their HRPP, policies and criteria for the disclosure and management of COIs. Minimally:

1. DHA personnel involved in the conduct of human subjects research are responsible for disclosing any actual or potential COIs at the time an activity is submitted for HRPP review. This includes any ombudsmen or research monitors, who must be independent of the study outside of those assigned roles;

2. Personnel who have identified an actual or potential COI are responsible for proposing a strategy for the mitigation or management of the conflict. Examples of conflict management strategies include, but are not limited to:

a. Disclosure of the COI to potential subjects during the informed consent process; and

b. The conflicted individual agrees not to participate in certain aspects of the conduct of the research (e.g., recruitment, consent, data analysis), etc.

3. The appropriate conflict management strategy depends on both the nature of the COI and the nature of the research, so acceptable strategies should not be limited to those listed herein or those listed in an institution's HRPP;

4. The HRPP review body (e.g., IRB, EDO) has the authority to approve, require changes in, propose an alternative, or disapprove the proposed conflict management strategy. All HRPP determinations about conflict management strategies that are not approved must include a justification for the determination that is communicated to the investigator; and

5. DHA personnel involved in the review and approval of human subjects research are responsible for disclosing any actual or potential COIs with a proposed activity as soon as possible after the conflict is identified.

(b) DHA personnel who are HRPP reviewers are not permitted to make determinations about protocols with which they have an actual or potential COI.

1. DHA personnel may participate in initial discussions about the protocols with which they have an actual or potential COI, acting as expert consultants to the HRPP review body that will be making the formal determination;

2. DHA personnel may not participate in or be present for the determination made about protocols with which they have disclosed an actual conflict of interest. For example, an IRB member with a COI may participate in the initial deliberation and answer questions about a protocol, but must recuse themselves (and may not count toward quorum) and leave the meeting room prior to the final deliberation and vote on the protocol; and

3. A single HRPP reviewer (e.g., EDO, HRPO, IRB member conducting primary or expedited review) may disclose a COI and pass the review of the protocol to a different HRPP reviewer. If the conflicted individual is the only appropriately delegated HRPP reviewer at the DHA institution, the review should be routed to DHA ORP.

(4) Adjudication.

(a) DHA institutions must establish a clear adjudication process for investigators who do not concur with the non-approval of the conflict management strategy by the HRPP review body;

(b) If a consensus between the investigator and the DHA institution/HRPP review body cannot be reached about the appropriate steps for mitigating an actual or potential COI, the investigator may appeal the HRPP's determination to DHA ORP;

(c) The appeal request must include a brief description of the research, a description of the COI, a description of the individual's role in the conduct of the research, a summary of the conflict mitigation strategies proposed by both the investigator and the HRPP review body, and an explanation of why the strategy proposed by the HRPP review body is unacceptable to the investigator;

(d) The investigator's appeal to DHA ORP may not be the first step in the appeal process; and

(e) DHA ORP's determination regarding the appropriate conflict mitigation strategy is final and may not be further appealed.

5. RECORD-KEEPING.

a. DHA institutions and IRBs are required to document and maintain records of their research and oversight activities;

b. Records including, but not limited to, the following list should be maintained by the institution or IRB of Record, as applicable:

(1) All study submissions including initial submissions, all lifecycle actions such as CRs, annual institutional progress reports, where applicable, modifications, reportable events, especially UPIRTSOs, compliance reports, and closure reports;

(2) IRB member reviewer notes and recommendations to the IRB (not to be confused with reviewer notes of common communications with the PI, such as reciprocal conversations);

(3) Documents relevant and in support of the protocol, including investigational new drug applications, drug or device information, advertisements, scripts, tools, and other IRB approved documents;

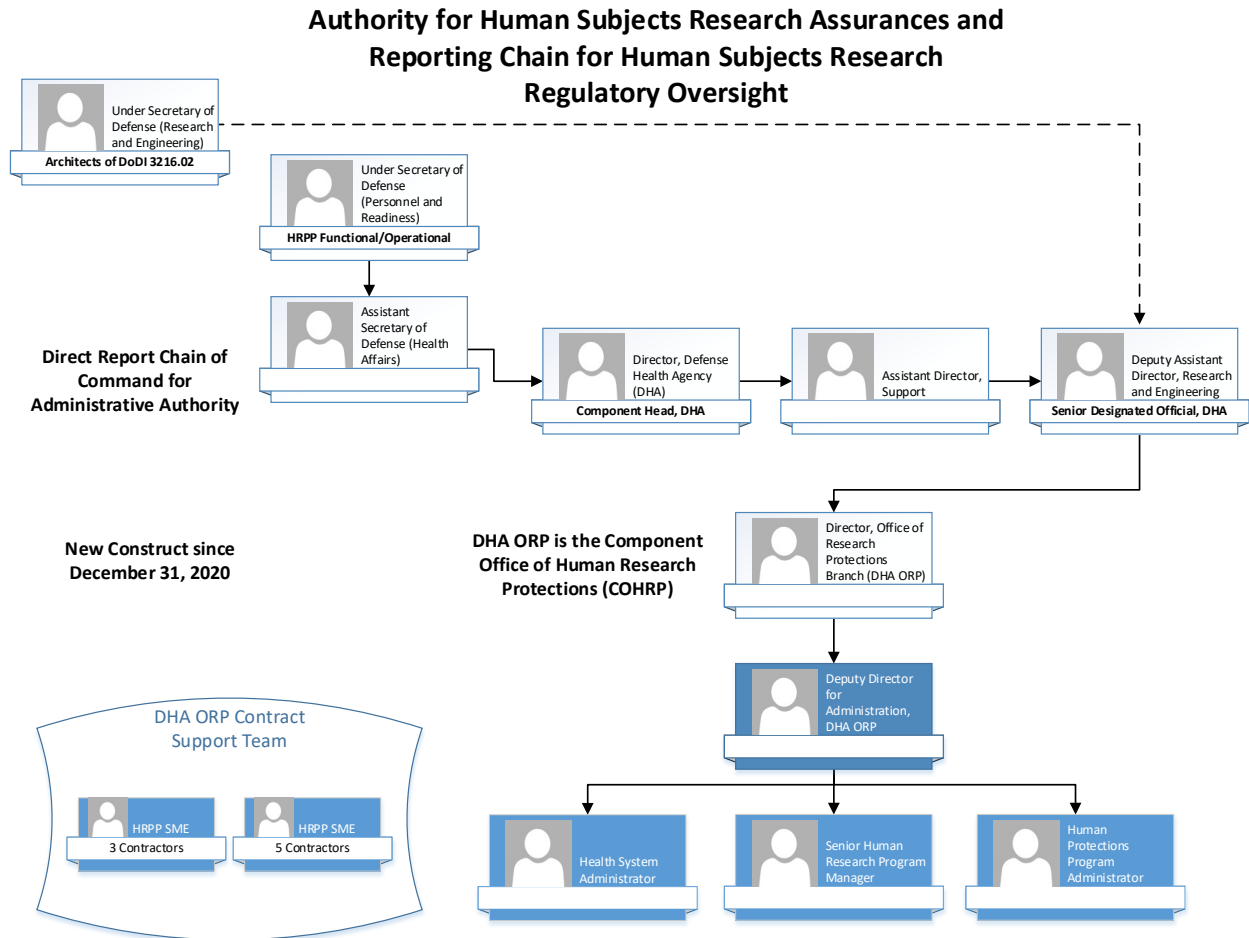
(4) Consent documents;

(5) IRB Meeting minutes;

- (6) Documentation of investigator and HRPP official training;
 - (7) All significant correspondence and/or notifications (including official HRPP determinations) between the HRPP office and investigators;
 - (8) EDO checklists and determinations and
 - (9) IRB membership rosters and member training records; and
 - (10) Any other documentation pertaining to the review of or conduct of a research study.
- c. All DHA institutions should document and maintain their research records in the web-based protocol management system identified by DHA ORP;
- d. Any paper and electronic filing system documentation of research records or activities, such as signed informed consent forms, should be maintained in a secure location onsite in accordance with local policy (as each institution and MTF should have a record retention policy completely separate from all de-identified research data, along with restricted access);
- e. Research records should be maintained and protected from destruction after study closure for the timelines indicated below:
- (1) Research records are required to be kept for at least 3 years after the completion of the research in accordance with Reference (e), Part 219 of Reference (f) and Reference (n);
 - (2) Research records that contain protected health information that may be covered by HIPAA are required to be kept for at least 6 years in accordance with Parts 252.235-7004 of Reference (y) and Reference (aa); and
 - (3) Records maintained by non-DoD institutions that document compliance or noncompliance with Reference (e) must be accessible for inspection and copying by authorized representatives of the DoD.
- f. Research records and oversight documentation should be maintained at the headquarters level in accordance with DHA Records Management Program (Part 2901 of Reference (z), Part 12 of Reference (aa), and References (ab) and (ac)); and
- g. Other federal regulations may require research records to be kept for longer than the timelines specified above. In any case of overlapping requirements, records should be maintained for the longer of the time periods, to include indefinitely.

APPENDIX 1

DHA ORP ORGANIZATION CHART



GLOSSARY

ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIO	Alternate Institutional Official
CLAR	Component Level Administrative Reviews
CoC	Certificate of Confidentiality
COHRP	Component Office of Human Research Protections
COI	conflict of interest
DAD	Deputy Assistant Director
DHA	Defense Health Agency
DHA-AI	Defense Health Agency-Administrative Instruction
DIO	Deputy Institutional Official
DOHRP	Department of Defense Office for Human Research Protections
EDO	Exemption Determination Official
FC	for cause
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HPA/HPD	Human Protections Administrator
HPD	Human Protections Director
HRPO	Human Research Protections Official
HRPP	Human Research Protection Program
IAIR	Institutional Agreement for Institutional Review Board Review
IIA	Individual Investigator Agreement
IO	Institutional Official
IRB	Institutional Review Board
LSGD	large-scale genomic data
MTF	Military Medical Treatment Facility
NCI	National Cancer Institute
NR	Not Research
ORP	Office of Research Protections
PI	principal investigator

R&E	Research and Engineering
RB	risk-based
RNIHS	Research Not Involving Human Subjects
SAV	Site Assistance/Assessment Visit
SDO	Senior Designated Official
sIRB	Single Institutional Review Board
SME	subject matter expert
SOP	standard operating procedures
UPIRTSO	unanticipated problems involving risks to subjects or others